IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR, INC., Plaintiff, v. DEY, L.P. and DEY, INC., Defendants.	)	C.A. No. 06-113-JJF (Consolidated)
SEPRACOR, INC., Plaintiff, v. BARR LABORATORIES, INC., Defendant.	)	**REDACTED PUBLIC VERSION**

DECLARATION OF SAM V. DESAI IN SUPPORT OF DEFENDANTS DEY, L.P. AND DEY, INC.'S OPENING CLAIM CONSTRUCTION BRIEF

(VOLUME III of III – EXS. 14-24)

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Dated: April 10, 2008

EXHIBIT 14

PN 7021931

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

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United States Patent and Trademark Office

August 04, 2006

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *09/466,107*
FILING DATE: *December 17, 1999*
PATENT NUMBER: *6,083,993*
ISSUE DATE: *July 04, 2000*

By Authority of the
Under Secretary of Commerce for Intellectual Property
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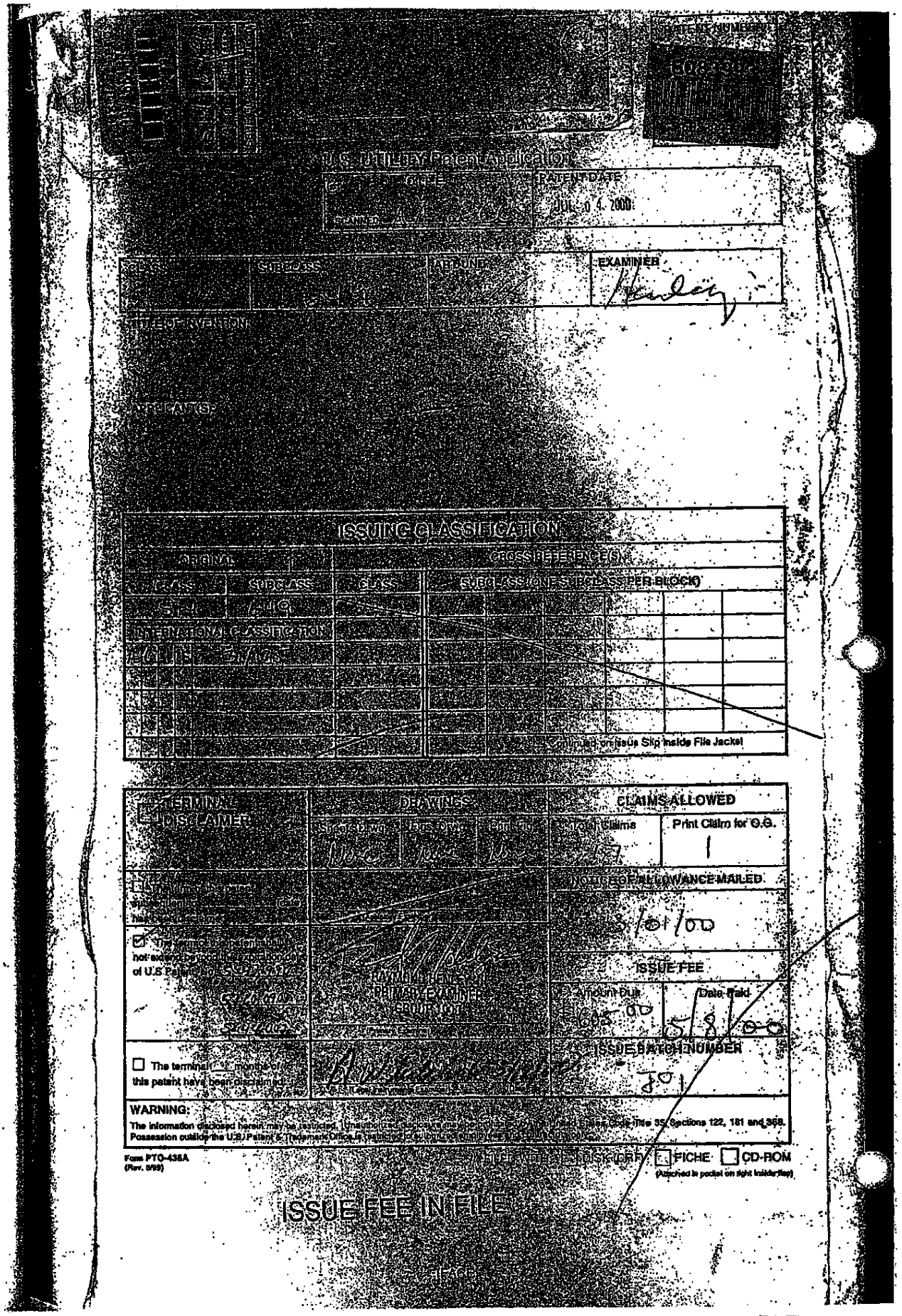
W. MONTGOMERY
Certifying Officer



U.S. UTILITY Patent Application

PATENT DATE

Jul. 04. 2000

EXAMINER

TITLE OF INVENTION

ISSUING CLASSIFICATION

CROSS REFERENCE(S)

INTERNATIONAL CLASSIFICATION

Mail on Issue Slip inside File Jacket

TERMINAL DISCLAIMER

DRAWINGS

CLAIMS ALLOWED

Total Claims

Print Claim for O.G.

NOTICE OF ALLOWANCE MAILED

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United States Patent [19]

Barberich et al.

[11] Patent Number: 6,083,993

[45] Date of Patent: *Jul. 4, 2000

[54] METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(−) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor Inc., Marlborough, Mass.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: 09/466,107

[22] Filed: Dec. 17, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/200,541, Nov. 25, 1998, which is a continuation of application No. 09/063,551, Apr. 21, 1998, Pat. No. 5,844,002, which is a continuation of application No. 08/691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of application No. 08/335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of application No. 07/896,725, Jun. 9, 1992, abandoned, which is a continuation of application No. 07/461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[7] A61K 31/135

[52] U.S. Cl. 514/649

[58] Field of Search 514/649

[56] References Cited

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[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

17 Claims, No Drawings

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of our prior copending application Ser. No. 09/200,541, filed Nov. 25, 1998, which is a continuation of application Ser. No. 09/063,551, filed Apr. 21, 1998, now U.S. Pat. No. 5,844,002, which was a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which was a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which was a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs.

In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of: α^1[(tert-butylamino) methyl]-4-hydroxy-mxylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine.

or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

11. A method according to claim 10, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

12. A method according to claim 10, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

13. A method according to claim 10, wherein the optically pure R(−) albuterol is administered by inhalation.

14. A method according to claim 13, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

15. A method according to claim 10, wherein the optically pure R(−) albuterol is administered orally.

16. A method according to claim 15, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

17. A method according to claim 15, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

* * * * *

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/466,107	12/17/99	514	1614	0701.027H

APPLICANT: TIMOTHY J BARBERICH, CONCORD, MA; JAMES W YOUNG, STILL RIVER, MA.

CONTINUING DOMESTIC DATA********

VERIFIED

THIS APPLN IS A CON OF 09/200,541 11/25/98
WHICH IS A CON OF 09/063,551 04/21/98 PAT 5,844,002
WHICH IS A CON OF 08/691,604 08/15/96 PAT 5,760,090
WHICH IS A CON OF 08/335,480 11/07/94 PAT 5,547,994
WHICH IS A CON OF 08/163,581 12/07/93 PAT 5,362,755
WHICH IS A CON OF 07/896,725 06/09/92 ABN
WHICH IS A CON OF 07/461,262 01/05/90 ABN

371 (NAT'L STAGE) DATA*******

VERIFIED

Mme A

FOREIGN APPLICATIONS********

VERIFIED

Mme A

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 02/05/00 ** SMALL ENTITY **

Foreign Priority claimed 35 USC 119 (a-d) conditions met	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐yes ☑no ☐yes ☐no ☐Met after Allowance and Acknowledged Examiner's initials _____ Initials	MA	0	17	2

PHILIP E HANSEN
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ALBANY NY 12203

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext.) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
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Bib Data Sheet

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SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/466,107	12/17/1999 RULE _	514	1614	0701.027H

APPLICANTS

TIMOTHY J BARBERICH, CONCORD, MA ;
JAMES W YOUNG, STILL RIVER, MA ;

** CONTINUING DATA **********

THIS APPLICATION IS A CON OF 09/200,541 11/25/1998
WHICH IS A CON OF 09/063,551 04/21/1998 PAT 5,844,002
WHICH IS A CON OF 08/691,604 08/15/1996 PAT 5,760,090
WHICH IS A CON OF 08/335,480 11/07/1994 PAT 5,547,994
WHICH IS A CON OF 08/163,581 12/07/1993 PAT 5,362,755
WHICH IS A CON OF 07/896,725 06/09/1992 ABN
WHICH IS A CON OF 07/461,262 01/05/1990 ABN

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENCE GRANTED ** SMALL ENTITY **
** 02/05/2000

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	MA	_	17	2
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged _____ Examiner's Signature _____ Initials				

ADDRESS

PHILIP E HANSEN
HESLIN AND ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY, NY12203

TITLE

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
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PATENT APPLICATION SERIAL NO._____

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PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

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01 FC:201 380.00 OP

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(5/87)
*U.S. GPO: 1998-433-214/80464

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12-20-99

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 0701.027H

Total Pages in this Submission 3

jc504 U.S. PTO 12/17/99

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

jc135 U.S. PTO 09/466107 12/17/99

and invented by:

Timothy J. Barberich and James W. Young

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/200,541

Which is a:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/063,551

Which is a:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 08/691,604

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 10 pages and including the following:
   - a. ☒ Descriptive Title of the Invention
   - b. ☐ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Microfiche Appendix *(if applicable)*
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☐ Brief Description of the Drawings *(if drawings filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL (Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 0701.027H

Total Pages in this Submission 3

Application Elements (Continued)

3. ☐ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☐ Formal b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☐ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☒ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche
7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*
   a. ☐ Paper Copy
   b. ☐ Computer Readable Copy
   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☒ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
    ☐ First Class ☒ Express Mail *(Specify Label No.):* EK083650148US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 0701.027H

Total Pages in this Submission 3

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☒ Small Entity Statement(s) - Specify Number of Statements Submitted: 1

17. ☐ Additional Enclosures *(please identify below):*

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	17	- 20 =	0	x $9.00	$0.00
Indep. Claims	2	- 3 =	0	x $39.00	$0.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$380.00
OTHER FEE *(specify purpose)*					$0.00
				TOTAL FILING FEE	$380.00

☒ A check in the amount of $380.00 to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 08-1935 as described below. A duplicate copy of this sheet is enclosed.

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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: December 17, 1999

Signature

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09465107.121799

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

In Re Application of: Barberich et al.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Attorney Docket No.: 0701.027H

"EXPRESS MAIL" MAILING LABEL NO. EK083650148US

Date of Deposit December 17, 1999

I hereby certify that this paper is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and addressed to Assistant Commissioner for Patents Washington, DC 20231

Robyn Dunlavey
(Typed or printed name of person mailing paper or fee)

Robyn Dunlavey
(Signature of person mailing paper or fee)

Enclosed:

1. Patent Application which includes: Specification (7 pgs.); 12 Claims (2 pgs.); and Abstract (1 pg.)
2. New Utility Patent Application Transmittal Letter (In duplicate)
3. Copy of Declaration for Patent Application
4. Check in the amount of $380 covering Filing Fee
5. Verified Statement Claiming Small Entity Status
6. Terminal Disclaimer
7. Preliminary Amendment (5 pgs.)
8. Acknowledgment Postcard

PC89-05
/4/90
AC16

PATENT APPLICATION
DOCKET NO: SB89-05

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Description

Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a

specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

Summary of the Invention

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is

administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

Detailed Description of the Invention

The present invention relies on the bronchodilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily

obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of

administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in

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tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine

experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation, said R isomer being substantially free of its S(+) isomer.

2. A method of Claim 1 wherein the amount of the R(-) isomer of albuterol is greater than approximately 90% by weight.

3. A method of Claim 2 wherein the amount of the R(-) isomer of albuterol is greater than 99% by weight.

4. A method of Claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(-) isomer of albuterol per dose.

5. A method of Claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(-) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation and at least one additional drug.

7. A method of Claim 6 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

8. A method of Claim 7 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

9. A composition comprising an optically pure R(-) isomer of albuterol and at least one additional drug.

10. A composition of Claim 9 containing at least 90% by weight of the R(-) isomer of albuterol.

11. A composition of Claim 10 containing at least 99% by weight of the R(-) isomer of albuterol.

12. A composition of Claim 9 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Abstract of the Disclosure

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

89-05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Declaration for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

the specification of which (check one)

☐ is attached hereto.

☒ was filed on January 5, 1990 as Application Serial No. 07/461,262 (if applicable). and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

(Number)	(Country)	(Day/Month/Year filed)	Priority Claimed Yes	No
			☐	☐
			☐	☐
			☐	☐

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing date)	(Status, patented, pending, abandoned)
(Application Serial No.)	(Filing date)	(Status, patented, pending, abandoned)

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

I also hereby grant additional Powers of Attorney to the following attorney(s) and/or agent(s) to file and prosecute an international application under the Patent Cooperation Treaty based upon the above-identified application, including a power to meet all designated office requirements for designated states.

David E. Brook	Registration No. 22,592
James M. Smith	Registration No. 28,043
Leo R. Reynolds	Registration No. 20,884
Giulio A. DeConti, Jr.	Registration No. 31,503
Richard A. Wise	Registration No. 18,041
Patricia Granahan	Registration No. 32,227
Mary Lou Wakimura	Registration No. 31,804
Thomas O. Hoover	Registration No. 32,470
Paula A. Campbell	Registration No. 32,503
Alice C. Olek	Registration No. 33,542

all of Hamilton, Brook, Smith and Reynolds, P.C., Two Militia Drive, Lexington, Massachusetts 02173;

and

_____

_____

Send correspondence to: Patricia Granahan, Esq.
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
Two Militia Drive, Lexington, Massachusetts 02173

Direct telephone calls to: Patricia Granahan, Esq.

617-861-6240

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Timothy J. Barberich

Inventor's Signature Timothy J. Barberich Date 2/25/90

Residence 73 Nashoba Road
Concord, Massachusetts 01742

Citizenship USA

Post Office Address SAME

Full name of second joint inventor, if any James W. Young

Second Inventor's Signature James W. Young Date 1 March 90

Residence 295 Still River Road
Still River, Massachusetts 01467

Citizenship USA

Post Office Address SAME

Full name of third joint inventor, if any

Third Inventor's Signature Date

Residence

Citizenship

Post Office Address

Full name of fourth joint inventor, if any

Fourth Inventor's Signature Date

Residence

Citizenship

Post Office Address

SPC89-C1

Applicant or Patentee: Timothy J. Barberich and James W. Young Attorney's
Serial or Patent No.: 07/461,262 Docket No.: SPC89-
Filed or Issued: January 5, 1990
For: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(c) - SMALL BUSINESS CONCERN

I hereby declare that I am

[ ] the owner of the small business concern identified below:

[X] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN Sepracor, Inc.

ADDRESS OF CONCERN 33 Locke Drive
Marlborough, MA 01752

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL by inventor(s) Timothy J. Barberich and James W. Young

described in

[ ] the specification filed herewith

[X] application serial no. 07/461,262, filed January 5, 1990

[ ] patent no. _____, issued _____

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9 (d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9 (d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____

ADDRESS _____

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME _____

ADDRESS _____

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Victor H. Woolley

TITLE OF PERSON OTHER THAN OWNER Vice President, Finance

ADDRESS OF PERSON SIGNING 33 Locke Drive, Marlborough, MA 01752

SIGNATURE _____ DATE _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich *et al.* Atty Dkt. No.: 0701.027H

Serial No.: Unknown
Continuation of 09/200,541
which was filed: November 25, 1998
Group Art Unit: 1614
Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

To: Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir:

Prior to examination, please amend the application as follows:

In the Title:

Please delete "METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL" and substitute therefor --METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(-)ALBUTEROL--.

In the specification:

Page 1, between line 2 and line 3, insert:

--Cross Reference to Related Applications

This application is a continuation of our prior copending application 09/200,541, filed November 25, 1998, which is a continuation of application 09/063,551, filed April 21, 1998, now US Patent 5,844,002, which was a continuation of application 08/691,604, filed August 15, 1996, now US Patent 5,760,090, which was a continuation of application 08/335,480, now US patent filed November 7, 1994,

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December 8, 1999

5,547,994, which was a continuation of application 08/163,581, filed December 7, 1993, now US patent 5,362,755, which was a continuation of application 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application 07/461,262, filed January 5, 1990, now abandoned.--

In the Claims:

Cancel claims 1-12.

Please add the following claims:

13. (New) A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

14. (New) A method according to Claim 13, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

15. (New) A method according to Claim 13, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

16. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered by inhalation.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of

about 30 μg to about 90 μg.

16. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered orally.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

18. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or syrup.

19. (New) A method according to Claim 17, wherein the optically pure R(-) albuterol is administered as a syrup.

20. (New) A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

21. (New) A method according to Claim 20, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

22. (New) A method according to Claim 20, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

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December 8, 1999

25. (New) A method according to Claim 22, wherein the optically pure R(-) albuterol is administered by inhalation.

26. (New) A method according to Claim 25, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

27. (New) A method according to Claim 22, wherein the optically pure R(-) albuterol is administered orally.

28. (New) A method according to Claim 27, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

29. (New) A method according to Claim 27, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or syrup.

REMARKS

The present application is a continuation of US application, serial number 09/200,541. Claims 1-12 were present in the original application 07/461,262, from which this application claims ultimate priority. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-29 are therefore pending in this continuation application.

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In previous applications in this series, claims have been allowed to "a method of treating asthma" (08/691,604), to "a method for inducing bronchodilation or providing relief of bronchospasms" (09/063,551) and to "a method of treating an acute attack of asthma" (08/335,480). Applicants respectfully submit that new claims 13-29 to "a method of treating bronchospasm in a patient with reversible obstructive airway disease" and to a method of preventing bronchospasm in a patient with reversible obstructive airway disease" are allowable with a terminal disclaimer for reasons of record in parent applications 09/063,551 and 08/691,604.

In order to expedite prosecution, Applicants enclose herewith terminal disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fees under 37 C.F.R. 1.20(d).

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: December 17, 1999

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December 8, 1999

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Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent	Docket No. 0701.027H

In Re Application Of: **Barberich et al.**

09/466,107

Serial No.	Filing Date	Examiner	Group Art Unit
Dock. No. 0701.027H	12/17/99	N/A	1614

Invention: **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL**

#3

Owner of Record: **Timothy J. Barberich and James W. Young**

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TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 5,547,994 . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Philip E. Hansen
Signature

Dated: December 17, 1999

Philip E. Hansen
Typed or Printed Name

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☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

P32/REV01

SUBJE : DECISION ON TERMINAL DISCLAIMI : INFORMAL FORM

DATE: 2-7-00 APPL. S.N.: 09/466,107

TO EXAMINER: R. Kenley ART UNIT: 1614

M. MONTGOMERY ROOM: 1E18 MAILROOM DATE: 12-17-99

AFTER FINAL YES ____ NO ✓ NUMBER OF T.D(S). FILED 3

INSTRUCTIONS: I have reviewed the submitted T.D. with the results as set forth below. If you agree, please use the appropiate form paragraphs identified by this informal memo in your next office action to notify applicant about the T.D. If you disagree with my analysis or have questions at all about the acceptability of the T.D., please see me or our Special Program Examiner. THIS MEMO IS AN INFORMAL, INTERNAL MEMO ONLY. IT MUST NOT BE MAILED TO APPLICANT, NOR SHOULD A COPY BE IN LEFT IN FILE.

[✓] The T.D. is PROPER and has been recorded. (See 14.23).

[ ] The T.D. is NOT PROPER and has not been accepted for the reason(s) checked below. (See 14.24).

[ ] The recording fee of $_____ has not been submitted nor is there any pre authorization in the application file to charge to a deposit account. (See 14.28.07)

[ ] Application Examiner has not processed T.D. fee. (See fee authorization).

[ ] This T.D. does not satisfy Rule 321(b)(3) in that the person who has signed the T.D. has not stated his/her interest (and/or the extent of the interest of the business entity represented by the signature) in the application/patent. (See 14.26 and 14.26.01).

[ ] The T.D. lacks the enforceable only during the common owership clause needed to overcome a double patenting rejection, Rule 321(c). (See 14.27, 14.27.01).

[ ] It is directed to a particular claims(s), which is not acceptable since "the disclaimer must be of a terminal portion of the term of the entire patent to be granted". MPEP 1490. (See 14.26, 14.26.02).

[ ] The person who signed the terminal disclaimer:
- [ ] has failed to state his/her capacity to sign for the business entity. (See 14.28).
- [ ] is not recognized as an officer of the assignee. (See 14.29 and possibly 14.29.01).

[ ] No documentary evidence of a chain of title from the original inventor(s) to assignee has been submitted, nor is the reel and frame specified as to where such evidence is recorded in the office. 37 CFR 3.73(b). (See 1140 O.G. 72). *NOTE:* This documentary evidence or the specifying of the reel and frame may be found in the T.D. or in a seperate paper submitted by applicant. (See 14.30).

[ ] No "statement" specifying that the evidentiary documents have been reviewed and that, to the best of the assignee's knowledge and belief the title is in the assignee seeking to take action. 37 CFR 3.73(b). (See 1140 O.G. 72) (See 14.31).

[ ] The T.D. is not signed. (See 14.26, 14.26.3). or 14.26.03 if TD is not signed by all the owners.

[ ] Attorney not of record in oath/decl. or a seperate paper filed appointing a new or associate attorney. (See 14.29.01).

[ ] The serial number of the application (or the number of the patent) which forms the basis for the double patenting is missing or incorrect. (See 14.32).

[ ] The serial number of this application (or the number of the patent in reexam or reissue case(s) being disclaimed is missing or incorrect. (See 14.26, 14.26.04 or 14.26.05).

[ ] The period disclaimed is incorrect or not specified. (See 14.27, 14.27.2 or 14.27.3)(For Samples 14.27.04 and 14.27.05)

[ ] Other: _____

[ ] Suggestion to request refund of $_____. (See 14.35, 14.36).

[ ] EXAMINER NOTE: IF APPLICATION IS IN CONDITION FOR ALLOWANCE ANY OF THE ABOVE INFORMALTIES MAY BE FAXED IN TO THE GROUP

FOR SAMPLE TERMINAL DISCLAIMERS AND CERTIFICATES:

[ ] Sample of a TD over a pending application and assignee Certificate (See 14.37).
[ ] Sample of a TD over a prior patent and assignee Certificate (See 14.38).
[ ] Sample Assignee Certificate under 37 CFR 3.73 (b) (See 14.39)

Notice of Allowability

Application No.	Applic...(s)
09/466,107	Timothy J. Barberich, et al.
Examiner	**Group Art Unit**
Ray Henley	1614

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *the application papers filed December 17, 1999*

☒ The allowed claim(s) is/are *13-29*

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

☒ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1*

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1600

Sheet 1 of 1

INFORMATION DISCLOSURE CITATION	Docket No. 0701.027D	Serial No. 09/466,107
	Applicant: Barberich et al.	
	Filing Date:	Group: 1614

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	Date	Country	Class	Subclass	Translation Yes	Translation No
	BA	2 255 503	1992	UK			X	
	BC	DE2128258	1983	Germany				X
	BD	1298494	1971	UK			X	

Other Documents (including Author, Title, Date, pertinent public. etc.)

	CA	Tan et al. "Stereoselective Disposition of Salbutamol Enantiomers..." Clin. Chem. 33, 1026 (1987)
	CB	Brittain et al. "Some observations on the β-adrenoceptor agonist..." Br. J. Pharmac. 48, 144-147 (1973)
	CC	Hartley et al. "Absolute Configuration of the Optical Isomers of Salbutamol" J. Med. Chem. 12, 995 (1971)
	CD	Hawkins et al. "Relative Potency of (-)- and (±)-Salbutamol on Guinea Pig..." J. Med. Chem. 16, 856-857 (1973)
	CE	Buckner et al. "Studies on the Effects of Enantiomers of Soterenol, Trimetoquinol..." J. Pharm. Exp. Ther. 189, 616-625 (1974)
	CF	Passowicz-Muszynska E. "Effect on beta adrenergic receptors of tachyphylaxis..." Index Medicus 91:164287
	CG	Pauwels "Effect of corticosteroids on the action of sympathomimetics" Index Medicus 86:051970
	CH	Chapman et al. "An anomalous effect of salbutamol in sensitised guinea pigs" Brit. J. Pharmacol 99, 66P (1990)
	CI	Morley et al. "Effects of (+) and racemic salbutamol on airway responses in the guinea pig" Brit. J. Pharmacol. 104, 295P (1991)
	CJ	Chapman et al. "Racemic mixtures at root of worsening symptoms? Active enantiomers..." TIPS 13, 231-232 (1992)
	CK	Huittari et al. "Comparison of acute bronchodilator effects of oral salbutamol,..." Chem. Abstr. 89: 123259m (1978)

Examiner [signature] Date Considered 3/1/08

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM17/0301

PHILIP E HANSEN
HESLIN AND ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
09/466,107	12/17/99	017	HENLEY III, R	1614	03/01/00

First Named Applicant	35 USC 154(b) term ext. =	
BARBERICH,	0 Days.	

TITLE OF INVENTION: METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 0701.027/H	514-649.000	J01	UTILITY	YES	$605.00	06/01/00

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or

B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

All communications regarding this application must give application number and batch number.
Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 10-95) Approved for use through 06/30/99. (0651-0033) *U.S. GPO: 1999-454-457/24501

DLEV012411

FILE COPY

0701.0271I

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 09/466,107 Group Art Unit: 1614

Filed: December 17, 1999 Examiner:

Title METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

Certificate of Facsimile Transmission

I hereby certify that this correspondence is being transmitted by facsimile to Assistant Commissioner for Patents, Application Processing Branch, Customer Correction Branch, Washington, D.C. 20231, Facsimile (703) 308-7751, on February 17, 2000.

Philip E. Hansen
Agent for Applicant
Registration No. 32,700

Date of Signature: February 17, 2000

To: Assistant Commissioner for Patents
Application Processing Branch
Customer Correction Branch
Washington, D.C. 20231

COMMUNICATION REQUESTING CORRECTION OF OFFICIAL FILING RECEIPT

Sir:

Applicant encloses a copy of the Official Filing Receipt issued in connection with the above-identified application.

The following error appears in the title:

"METHOD FOR TREATING BRONCHOSPASM USING OPTICALL PURE R (-) ALBUTEROL"

N:\USERS\STAFF\RFP\SEPRACOR\0271I.cor
February 17, 2000

should read

--METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL--

A copy of the Filing Receipt is enclosed herewith. The error in the receipt has been circled. Applicant hereby requests that a Corrected Official Filing Receipt indicating the correct title be issued.

Respectfully submitted,

Philip E. Hansen
Agent for Applicant
Registration No. 32,700

Dated: February 17, 2000

HESLIN & ROTHENBERG, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

N:\USERS\STAFF\RFD\SEPRACOR\627H.cor
February 17, 2000

PTO-103A
(Rev. 8-98)

FILING RECEIPT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
09/466,107	12/17/99	1614	$380.00	0701.027H	0	17	2

PHILIP B HANSEN
HESLIN AND ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts of Application" ("Missing Parts Notice") in this application, please submit any corrections to this Filing Receipt with your reply to the "Missing Parts Notice." When the PTO processes the reply to the "Missing Parts Notice," the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s) TIMOTHY J BARBERICH, CONCORD, MA; JAMES W YOUNG, STILL RIVER, MA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A CON OF 09/200,541 11/25/98
WHICH IS A CON OF 09/063,551 04/21/98 PAT 5,844,002
WHICH IS A CON OF 08/691,604 08/15/96 PAT 5,760,090
WHICH IS A CON OF 08/335,480 11/07/94 PAT 5,547,994
WHICH IS A CON OF 08/163,581 12/07/93 PAT 5,362,755
WHICH IS A CON OF 07/896,725 06/09/92 ABN
WHICH IS A CON OF 07/461,262 01/05/90 ABN

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 02/05/00 ** SMALL ENTITY **
TITLE
METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

PRELIMINARY CLASS: 514

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FEB -9 2000
HESLIN & ROTHENBERG

DATA ENTRY BY: GUNTER-WARREN, JOYCE TEAM: 06 DATE: 02/05/00

Pubs

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                    *** APPLICATION INFORMATION DISPLAY ***
                      03/27/00  14:50          DETAIL          CONTENTS:
YSN:  09/466107                              INFORMATION:       10 N/=. N 03/01/00
DT:   12/17/99                                                  09 CNTA F 03/01/00
TNO:                PUBNO:                          F466107     08 DISQ C 02/28/00
SDT:  00/00/00      PUBDT:  00/00/00                            07 DIST I 12/17/99
NDT:  00/00/00      PGPUB CL/SC:     /                          06 DOCK D 02/09/00
AL:   BARBERICH                    ET AL                        05 A.PE I 12/17/99
T:    7560  LOCDT:  03/22/00   BATNO:  J01                      04 OIPE I 02/07/00
R-LOC:              IE TEAM:  00   ISSNO:  00                   03 SCAN E 01/19/00
ATO-NAME:  NO NAME FOUND                                        02 ZZZZ L 01/20/00
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GP CD:  N/=.  START DT:  03/01/00  DUE DT:    06/01/00                    / /
MR NO/NAME:  66553/HENLEY III, RAYMOND                                    / /
CKET DATE:  02/09/00  GAU:  1614    L R CD:  01                           / /
TY DOCK #:  0701.027H     LOST  N   LOST DT  00/00/00                    / /
PLN TYPE:  2  TYPE SM ENT:  3   UNMAT PET:  N                            / /
RR CL/SC:  514/649.000  FOR PRIOR CL:  N  PET FAOM:                       / /
TLE OF INVENTION:   UNAVAIL FOR ACTION:  N  PP UNAVAIL:    0
ETHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

D OF DISPLAY                  TO DISPLAY CONTENTS:  PUSH SEND
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7560

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

CHANGE OF ADDRESS/POWER OF ATTORNEY

LE LOCATION 9200 SERIAL NUMBER 09466107 PATENT NUMBER 6083993

THE CORRESPONDENCE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 23405

THE PRACTITIONERS OF RECORD HAVE BEEN CHANGED TO CUSTOMER # 23405

THE FEE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 23405

ON 09/20/01 THE ADDRESS OF RECORD FOR CUSTOMER NUMBER 23405 IS:

HESLIN ROTHENBERG FARLEY & MESITI PC
5 COLUMBIA CIRCLE
ALBANY NY 12203

AND THE PRACTITIONERS OF RECORD FOR CUSTOMER NUMBER 23405 ARE:

778 26429 31789 31833 32700 32782 35670 36632 36650 39115
331 39946 41707 41779 44589 46747 46787

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THIS FILE IS ASSIGNED TO GAU 1614.

PTO-FMD
TALBOT-1/97

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
09/466,107	6083993	1614	9200 J 10051 1015 12

Change of Address/Power of Attorney

The following fields have been set to Customer Number 2264 on 02/28/2005

- Correspondence Address
- Power of Attorney
- Maintenance Fee Address

The address of record for Customer Number 2264 is:
HESLIN ROTHENBERG FARLEY & MESIRI P.C.
5 COLUMBIA CIRCLE
ALBANY, NY 12203

The Practitioners of record for Customer Number 2264 are:

PTO INSTRUCTIONS:

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2) Put a line through the old address on the File Jacket and enter the Customer Number as the new address.
3) File this Notice in the File Jacket.

Please take the following action when the correspondence address has NOT been changed:
1) File this Notice in the File Jacket

Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent	Docket No. 0701.027H

In Re Application Of: **Barberich et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
Dock. No. 0701.027H	12/17/99	N/A	1614

Invention: **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL**

Owner of Record: **Timothy J. Barberich and James W. Young**

/2000 MSHIFERA 00000010 09466107

:248 55.00 OP

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 5,844,002 . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Signature Dated: December 17, 1999

Philip E. Hansen
Typed or Printed Name

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

P32/REV01

Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent	Docket No. 0701.027H

In Re Application Of: **Barberich et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
Dock. No. 0701.027H	12/17/99	N/A	1614

Invention: **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL**

Owner of Record: **Timothy J. Barberich and James W. Young**

02/2000 NSHIFERA 00000010 09456107
01:248 55.00 OP

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a **100** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. **5,760,090**. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Signature Dated: **December 17, 1999**

Philip E. Hansen
Typed or Printed Name

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MAIL ROOM

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

PS2/REV01

PART B—ISSUE FEE TRANSMITTAL

Complete and mail this form, together with applicable fees, to: Box ISSUE FEE
Assistant Commissioner for Patents
Washington, D.C. 20231

B/P

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Issue Fee receipt, the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

Note: The certificate of mailing below can only be used for domestic mailings of the Issue Fee Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

HM12/0301
PHILIP E HANSEN
HESLIN AND ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

Certificate of Mailing

I hereby certify that this Issue Fee Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

Philip E. Hansen (Depositor's name)
(Signature)
May 4, 2000 (Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
09/466,107	12/17/99	017	HENLEY III, R	1614	03/01/00

First Named Applicant: BARBERICH, 35 USC 154(b) term ext. = 0 Days.

TITLE OF INVENTION: METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R (-) ALBUTEROL

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 0701.027H	514-649.000	J01	UTILITY	YES	$605.00	06/0

Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Heslin & Rothenberg, P.C.
2
3

ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Sepracor Inc.

(B) RESIDENCE: (CITY & STATE OR COUNTRY) Marlborough, MA

Please check the appropriate assignee category indicated below (will not be printed on the patent)
☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):
☒ Issue Fee
☒ Advance Order - # of Copies 10

4b. The following fees or deficiency in these fees should be charged to:
DEPOSIT ACCOUNT NUMBER 08-1935
(ENCLOSE AN EXTRA COPY OF THIS FORM)
☐ Issue Fee
☐ Advance Order - # of Copies

The COMMISSIONER OF PATENTS AND TRADEMARKS IS requested to apply the Issue Fee to the application identified above.

Authorized Signature: Philip E Hansen (Date) 05/4/00

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

05/09/2000 STEFFER1 00000098 09466107
01 FC:242 605.00 OP
02 FC:561 30.00 OP

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE

PTOL-85B (REV.10-96) Approved for use through 06/30/98. OMB 0651-0033 Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DLEV012420

Express Mail Label No. EK083650?? US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)
(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 0701.027H

Total Pages in this Submission 3

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

and invented by:

Timothy J. Barberich and James W. Young

1c135 U.S. PTO 10/456117 12/17/99

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/200,541

Which is a:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/063,551

Which is a:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 08/691,604

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 10 pages and including the following:
   - a. ☒ Descriptive Title of the Invention
   - b. ☐ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Microfiche Appendix *(if applicable)*
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☐ Brief Description of the Drawings *(if drawings filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
0701.027H

Total Pages in this Submission
3

Application Elements (Continued)

3. ☐ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☐ Formal b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☐ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☒ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche
7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*
   a. ☐ Paper Copy
   b. ☐ Computer Readable Copy
   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☒ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
    ☐ First Class ☒ Express Mail *(Specify Label No.)*: EK083650148US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 0701.0271[illegible]

Total Pages in this Submission 3

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☒ Small Entity Statement(s) - Specify Number of Statements Submitted: 1

17. ☐ Additional Enclosures *(please identify below):*

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	17	- 20 =	0	x $9.00	$0.00
Indep. Claims	2	- 3 =	0	x $39.00	$0.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$380.00
OTHER FEE *(specify purpose)*					$0.00
				TOTAL FILING FEE	$380.00

☒ A check in the amount of $380.00 to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 08-1935 as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: December 17, 1999

Signature

Philip E. Hansen
Reg. No. 32,700
HESLIN & ROTHENBERG, P.C.
5 Columbia Circle
Albany, NY 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

cc:

HESLIN & ROTHENBERG, P. C.
ATTORNEYS AT LAW
5 COLUMBIA CIRCLE.
ALBANY, NEW YORK 12203

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PB METER 8152739

Box ISSUE FEE
Assistant Commissioner for Patents
Washington, D.C. 20231

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Class	Sub.	Date	Exmr.
514	649	3/1/00	TD

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
514	649	3/1/00	TD

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

Date	Exmr.

(RIGHT OUTSIDE)

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O.I.P.E. CLASSIFIER			1-5
FORMALITY REVIEW	[illegible]	67718	2/5/00
RESPONSE FORMALITY REVIEW			

INDEX OF CLAIMS

✔ ..... Rejected
= ..... Allowed
– (Through numeral)... Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal.
O ..... Objected

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PATENT APPLICATION

09466107

jc135 U.S. PTO
09/466107
12/17/99

JAN 8 00

CONTENTS

	Date Received (Incl. C. of M.) or Date Mailed		Date Received (Incl. C. of M.) or Date Mailed
1. ~~Application~~ papers		42.	
2. Terminal Disc.	12/17/99	43.	
3. Terminal Disc (S)	12-17-99	44.	
4. Lic. Allow.	03-01-00	45.	
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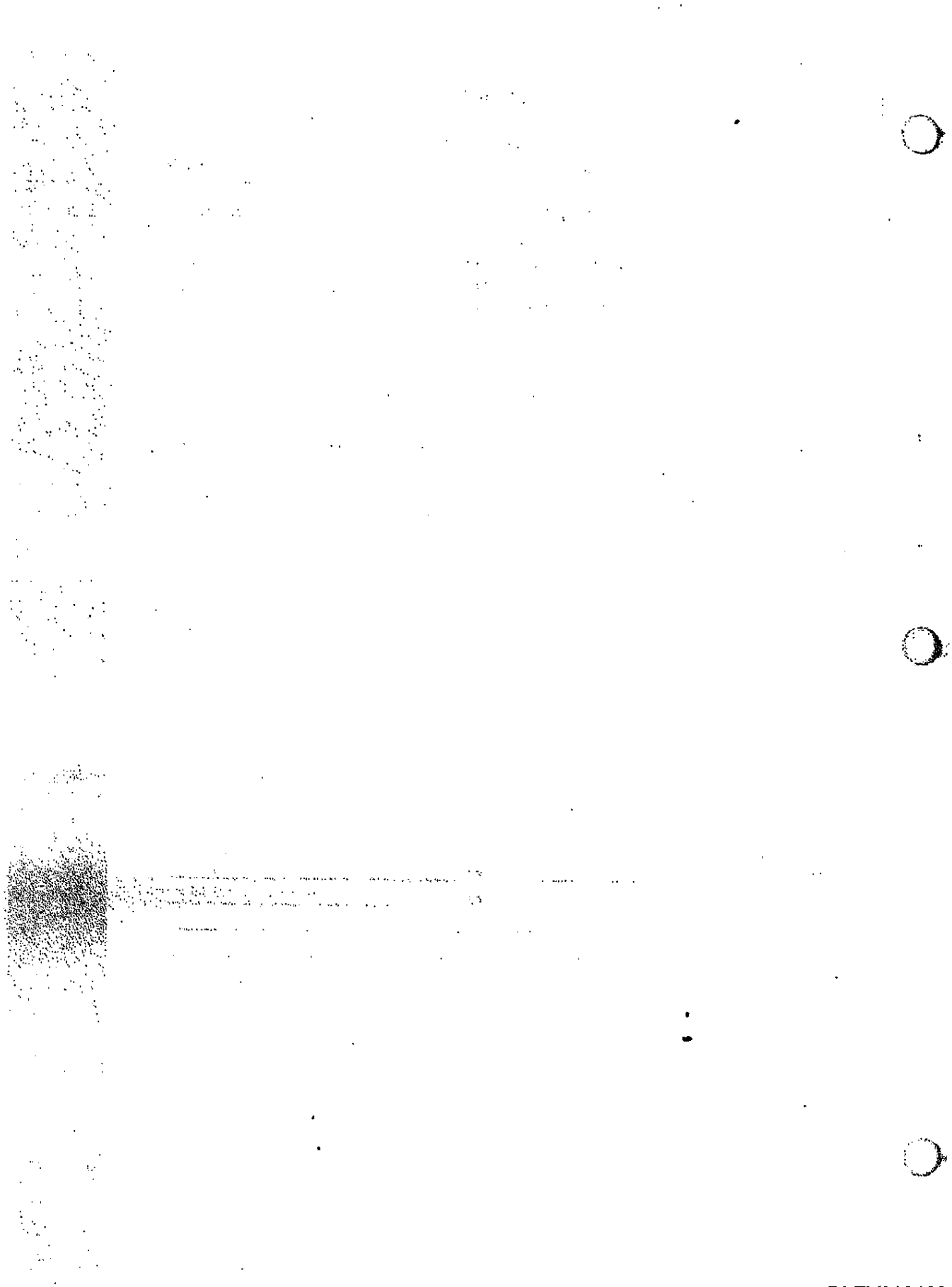

EXHIBIT 15

REDACTED

EXHIBIT 16

REDACTED

EXHIBIT 17

REDACTED

EXHIBIT 18

ILLUSTRATED
Stedman's MEDICAL DICTIONARY
24TH EDITION

WILLIAMS & WILKINS
Baltimore/London

Made in the United States of America

24th Edition, 1982
Reprinted 1983, 1984
English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978
Translated Editions
Greek 1976
Indian 1977
Japanese 1977
Portuguese 1976
Spanish (in press)

Library of Congress Cataloging in Publication Data

Stedman, Thomas Lathrop, 1853–1938.
Stedman's Medical dictionary.

1. Medicine—Dictionaries. I. Title. II. Title: Medical dictionary. [DNLM: 1. Dictionaries, Medical. W 13 S812m]
R121.S8 1982 610'.3'21 81-3021
ISBN 0-683-07915-8 AACR2

Composed and printed at the
Waverly Press, Inc.
Mt Royal and Guilford Aves.
Baltimore, MD 21202, U.S.A.

bronchiolitis

b. fibro'sa oblit'erans, obstruction of bronchioles, especially terminal bronchioles, by fibrous granulation tissue arising from ulcerated mucosa; the condition may follow inhalation of irritant gases, or may complicate pneumonia.

proliferative b., b. with obliteration of bronchiolar lumen and alveoli by epithelial proliferation, which may follow influenza and giant-cell pneumonia.

bronchiolo- [L. *bronchiolus, q.v.*]. Combining form relating to the bronchiolus.

bron'chiolopul'monary. Relating to the bronchioles and the lungs.

bronchiolus, pl. **bronchioli** (brong-ki'o-lus, brong-ki'o-lī) [Mod. L. dim. of *bronchus*]. [NA]. Bronchiole; one of the finer subdivisions of the bronchial tubes, less than 1 mm in diameter, and having no cartilage in its wall, but relatively abundant smooth muscle and elastic fibers.

bronchi'oli respirato'rii [NA], respiratory bronchioles; the smallest bronchioles (0.5 mm in diameter) that connect the terminal bronchioles to alveolar ducts; alveoli rise from part of the wall.

b. termina'lis, terminal *bronchiole.*

bronchiosteno'sis. Narrowing of the lumen of a bronchial tube.

bronchit'ic. Relating to bronchitis.

bronchitis (brong-kī'tis). Inflammation of the mucous membrane of the bronchial tubes.

asthmatic b., b. which aggravates an existing asthma.

capillary b., bronchiolitis.

Castellani's b., hemorrhagic b.

chronic b., a condition of the bronchial tree characterized by cough, hypersecretion of mucus, and expectoration of sputum over a long period of time, associated with increased vulnerability to bronchial infection; it is due to inhalation, over a prolonged period, of air contaminated by dust or by noxious gases which are mostly the products of combustion.

croupous b., fibrinous b.

fibrinous b., pseudomembranous, croupous, or plastic b.; inflammation of the bronchial mucous membrane, accompanied by a fibrinous exudation which often forms a cast of the bronchial tree.

hemorrhagic b., Castellani's b.; bronchopulmonary spirochetosis; bronchospirochetosis; a chronic b. due to infection with spirochetes (though other bacteria are usually present and contribute to the infection); the chief symptoms are cough and bloody sputum.

infectious avian b., a specific infectious disease of young birds, caused by infectious bronchitis virus and associated with blocking of respiratory passages by exudate; it is highly transmissible and often causes heavy losses of young chicks, and heavy production losses among older, laying birds.

obliterative b., b. oblit'erans, a fibrinous b. in which the exudate is not expectorated but becomes organized, obliterating the affected portion of the bronchial tubes.

plastic b., fibrinous b.

pseudomembranous b., fibrinous b.

putrid b., b. accompanied by an expectoration of foul smelling material.

summer b., see rose *cold;* hay *fever.*

verminous b., hoose; b. and bronchopneumonia caused by invasion of the bronchi by lungworms; occurs commonly in cattle, swine, and sheep, but rarely in other species.

bronchium, pl. **bronchia** (brong'kī-um, brong'kī-ah) [Mod. L. fr. G. *bronchion*]. A bronchial tube.

broncho- [G. *bronchos,* windpipe. BRONCH-]. Combining form denoting bronchus, and, in ancient usage, the trachea.

bronchoalveolar (brong-ko-al-ve'o-lar). Bronchovesicular.

bronchocavernous (brong-ko-kav'er-nus). Relating to a bronchus or bronchial tube and a pulmonary pathologic cavity.

bronchocele (brong'ko-sēl) [broncho- + G. *kēlē,* hernia]. Bronchiocele; a circumscribed dilation of a bronchus.

bronchoconstric'tion. Reduction in the caliber of a bronchus or bronchi.

bronchoconstrictor (brong-ko-kon-strik'tor). 1. Causing a reduction in caliber of a bronchus or bronchial tube. 2. An agent that possesses this action.

bronchodilatation (brong'ko-dil-ă-ta'shun). Bronchodilation; increase in caliber of the bronchi and bronchioles in response to pharmacologically active substances or autonomic nervous activity.

bronchodilation (brong'ko-di-la'shun). 1. Rarely used synonym for bronchiectasis. 2. Sometimes used as an alternative spelling for bronchodilatation.

bronchodilator (brong-ko-di-la'tor). 1. Causing an increase in caliber of a bronchus or bronchial tube. 2. An agent that possesses this power.

bronchoedema (brong'ko-ĕ-de'mah). Swelling of the mucosa of the bronchi.

bron'choesophagol'ogy [broncho- + G. *oisophagos,* esophagus, + *logos,* study]. The specialty concerned with peroral endoscopic examination of the esophagus and tracheobronchial tree.

bron'choesophagos'copy. Examination of the tracheobronchial tree or esophagus through appropriate endoscopes.

bronchofiberscope (brong-ko-fī'ber-skōp). A fiberoptic endoscope particularly adapted for visualization of the trachea and bronchi.

bronchogenic (brong-ko-jen'ik). Bronchiogenic.

bron'chogram. The radiogram obtained at bronchography.

bronchography (brong-kog'ră-fī) [broncho- + G. *graphē,* a drawing]. Radiographic examination of the tracheobronchial tree by the injection of one of several radiopaque materials.

broncholith (brong'ko-lith) [broncho- + G. *lithos,* stone]. Bronchial calculus; a hard concretion in a bronchus or bronchial tube.

bron'cholithi'asis. Bronchial inflammation or obstruction caused by broncholiths.

bronchomalacia (brong'ko-mă-la'shī-ah) [broncho- + G. *malakia,* a softening]. Degeneration of elastic and connective tissue of bronchi and trachea.

bronchomo'tor. 1. Causing a change in caliber, dilation, or contraction of a bronchus or bronchiole. 2. An agent that possesses this action.

bronchomycosis (brong-ko-mi-ko'sis) [broncho- + G. *mykēs,* fungus]. Any fungus disease of the bronchial tubes or bronchi.

bronchophony (brong-kof'o-nī) [broncho- + G. *phōnē,* voice]. Bronchiloquy; bronchial voice; exaggerated vocal resonance heard over a bronchus surrounded by consolidated lung tissue. See also tracheophony.

whispered b., whispering *pectoriloquy.*

bronchoplasty (brong'ko-plas-tī) [broncho- + G. *plassō,* to form]. Surgical alteration of the configuration of a bronchus.

bronchopneumonia (brong'ko-nu-mo'nī-ah). Bronchial pneumonia; acute inflammation of the walls of the smaller bronchial tubes, with irregular areas of consolidation due to spread of the inflammation into peribronchiolar alveoli and the alveolar ducts; may become confluent or may be hemorrhagic; complications include necrosis and abscess formation.

tuberculous b., an acute form of pulmonary tuberculosis.

bronchopulmonary (brong-ko-pul'mo-nĕr-ī). Relating to the bronchial tubes and the lungs.

bronchorrhaphy (brong-kor'ă-fī) [broncho- + G. *raphē,* a seam]. Suture of a wound of the bronchus.

bronchorrhea (brong'ko-re'ah) [broncho- + G. *rhoia,* a flow]. Excessive secretion of mucus from the bronchial mucous membrane.

bronchoscope (brong'ko-skōp) [broncho- + G. *skopeō,* to view]. An endoscope for inspecting the interior of the tracheobronchial tree, either for diagnostic purposes (including biopsy) or for the removal of foreign bodies.

bronchoscopy (brong-kos'ko-pī). Inspection of the interior of the tracheobronchial tree through a bronchoscope.

bronchospasm (brong'ko-spazm). Contraction of smooth muscle in the walls of the bronchi and bronchioles, causing narrowing of the lumen.

EXHIBIT 19

CHRONOLOGY OF THE PROSECUTION HISTORY

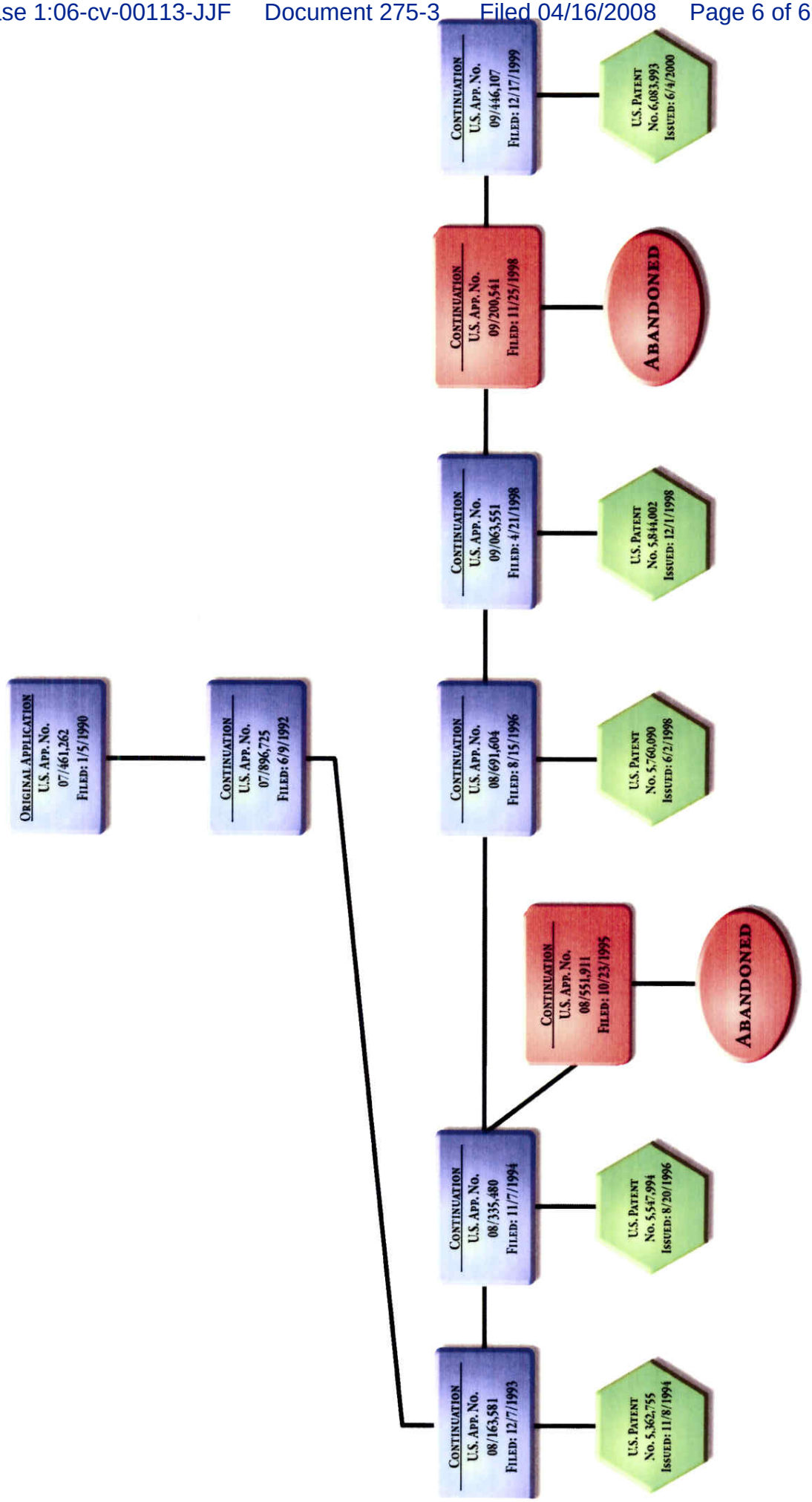

EXHIBIT 20

Subclass	ISSUE CLASSIFICATION
Class	

[redacted]

PATENT NUMBER

U.S. UTILITY PATENT APPLICATION

ABANDONED

O.I.P.E.	PATENT DATE
SCANNED 02 Q.A. 05	

SECTOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
	514	449	1614	

FILED WITH: ☐ DISK (CRF) ☐ FICHE
(Attached in pocket on right inside flap)

PREPARED AND APPROVED FOR ISSUE

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
			☐ Continued on Issue Slip inside File Jacket

☐ TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
☐ a) The term of this patent subsequent to _____ (date) has been disclaimed.	(Assistant Examiner) (Date)			NOTICE OF ALLOWANCE MAILED	
☐ b) The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____	(Primary Examiner) (Date)			ISSUE FEE	
				Amount Due	Date Paid
☐ c) The terminal ____months of this patent have been disclaimed.	(Legal Instruments Examiner) (Date)			ISSUE BATCH NUMBER	

Form PTO-436A
(Rev. 8/98)

(LABEL AREA)

(FACE)

jc510 U.S. PTO
09/200541
11/25/98

PATENT APPLICATION
09200541

INITIALS 12/7/99-SS

ABANDONED

CONTENTS

	Date received (Incl. C. of M.) or Date Mailed		Date received (Incl. C. of M.) or Date Mailed
1. Application ____ papers.		42.	
2. Re Amdt A	1/19/99	43.	
3. I. D. S.	1/19/99	44.	
4. Ltr. 3 mo.	9-17-99	45.	
5. CFR	9/3/99	46.	
6. Notice of Abnd.	4/26/00	47.	
7. Request for Acces	2/20/01	48.	
8. Request for Access 8-28-01		49.	
9. Request for Access 11-20-02		50.	
10. Request for Access 3/6/03		51.	
11. Request for Access 6-26-03		52.	
12. Request for Access 8/14/03		53.	
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ISSUE SLIP STAPLE AREA (for additional cross references)

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FORMALITY REVIEW			
		5988	1-13-89

INDEX OF CLAIMS

✔ ..... Rejected
= ..... Allowed
— (Through numeral)... Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim	Date		Claim	Date		Claim	Date	
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[redacted]

SEARCHED

Class	Sub.	Date	Exmr.
514	653	9/11/99	KA

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

Date	Exmr.

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

(RIGHT OUTSIDE)

DLEV011547

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

12/07/1998 NVILLARI 00000014 081935 09200541
01 FC:101 380.00 CH 380.00 OP

Adjustment date: 02/11/2000 RTSEGAYE
12/07/1998 NVILLARI 00000014 081935 09200541
01 FC:101 380.00 CR -380.00 OP

02/11/2000 RTSEGAYE 00000003 09200541
01 FC:201 380.00 OP

PTO-1556
(5/87)

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/200,541	11/25/98	514	1614	0701.27G

APPLICANT: TIMOTHY J. BARBERICH, CONCORD, MA; JAMES W. YOUNG, STILL RIVER, MA.

CONTINUING DOMESTIC DATA********
VERIFIED
THIS IS A CON OF 09/063,551 04/21/98 PAT 5844002
WHICH IS A CON OF 08/691,604 08/13/96
WHICH IS A CON OF 08/325,480 11/07/94

371 (NAT'L STAGE) DATA********
VERIFIED

FOREIGN APPLICATIONS********
VERIFIED

FOREIGN FILING LICENSE GRANTED 01/14/99

Foreign Priority claimed 35 USC 119 (a-d) conditions met	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐yes ☐no ☐Met after Allowance Verified and Acknowledged, Examiner's Initials	MA	0	12	2

ADDRESS:
PATRICIA GRANAHAN
HAMILTON BROOK SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON MA 02173

TITLE: ~~Formulations~~
METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
$760	No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Express Mail Label No. EL254627116US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
0701.027G
Total Pages in this Submission
3

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

and invented by:

Timothy J. Barberich and James W. Young

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/063,551 (4-21-98)

Which is a:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 08/691,604 (8-15-96)

Which is a:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 08/335,480 (11-07-94)

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 10 pages and including the following:
   - a. ☒ Descriptive Title of the Invention
   - b. ☐ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Microfiche Appendix *(if applicable)*
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☐ Brief Description of the Drawings *(if drawings filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
0701.027G
Total Pages in this Submission
3

Application Elements (Continued)

3. ☐ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☐ Formal b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☐ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☒ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche
7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*
   a. ☐ Paper Copy
   b. ☐ Computer Readable Copy
   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
    ☐ First Class ☒ Express Mail *(Specify Label No.)*: EL254627111US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
8701.027G

Total Pages in this Submission
3

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Small Entity Statement(s) - Specify Number of Statements Submitted: _____

17. ☐ Additional Enclosures *(please identify below):*

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	12	- 20 =	0	x $11.00	$0.00
Indep. Claims	3	- 3 =	0	x $41.00	$0.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$380.00
OTHER FEE *(specify purpose)* _____					$0.00
				TOTAL FILING FEE	$380.00

☒ A check in the amount of $380.00 to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 08-1935 as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: November 25, 1998

Philip E. Hansen
Reg. No. 32,700

Heslin & Rothenberg, P.C.
5 Columbia Circle
Albany, New York 12203

cc:

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

In Re Application of: Barberich et al.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Attorney Docket No.: 0701.027G

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Date of Deposit November 25, 1998

I hereby certify that this paper is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and addressed to Assistant Commissioner for Patents Washington, DC 20231

Jefry A. Capasso
(Typed or printed name of person mailing paper or fee)

Jefry A. Capasso
(Signature of person mailing paper or fee)

Enclosed:

1. Patent Application which includes: Specification (7 pgs.); 12 Claims (2 pgs.); and Abstract (1 pg.)
2. New Utility Patent Application Transmittal Letter (In duplicate)
3. Copy of Declaration for Patent Application
4. Check in the amount of $380 covering Filing Fee
5. Information Disclosure Citation
6. Postcard

C89-05
4/90
C16

PATENT APPLICATION
DOCKET NO: SPC89-05

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Description

Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prima action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a

specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

Summary of the Invention

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is

administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

Detailed Description of the Invention

The present invention relies on the bronchodilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^{1}[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily

obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of

administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in

tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine

experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation and at least one additional drug.

7. A method of Claim 6 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

8. A method of Claim 7 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

9. A composition comprising an optically pure R(-) isomer of albuterol and at least one additional drug.

10. A composition of Claim 9 containing at least 90% by weight of the R(-) isomer of albuterol.

11. A composition of Claim 10 containing at least 99% by weight of the R(-) isomer of albuterol.

12. A composition of Claim 9 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

Add a!

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Abstract of the Disclosure

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Declaration for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)

ALBUTEROL

the specification of which (check one)

☐ is attached hereto.

☒ was filed on January 5, 1990 as Application Serial No. 07/461,262 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing date)	(Status, patented, pending, abandoned)
(Application Serial No.)	(Filing date)	(Status, patented, pending, abandoned)

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

I also hereby grant additional Powers of Attorney to the following attorney(s) and/or agent(s) to file and prosecute an international application under the Patent Cooperation Treaty based upon the above-identified application, including a power to meet all designated office requirements for designated states.

David E. Brook	Registration No. 22,592
James M. Smith	Registration No. 28,043
Leo R. Reynolds	Registration No. 20,884
Giulio A. DeConti, Jr.	Registration No. 31,503
Richard A. Wise	Registration No. 18,041
Patricia Granahan	Registration No. 32,227
Mary Lou Wakimura	Registration No. 31,804
Thomas O. Hoover	Registration No. 32,470
Paula A. Campbell	Registration No. 32,503
Alice C. Olek	Registration No. 33,542

all of Hamilton, Brook, Smith and Reynolds, P.C., Two Militia Drive, Lexington, Massachusetts 02173;

and

_____

_____

Send correspondence to: Patricia Granahan, Esq.
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
Two Militia Drive, Lexington, Massachusetts 02173

Direct telephone calls to: Patricia Granahan, Esq.
617-861-6240

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Timothy J. Barberich
Inventor's Signature [signature] Date 2/28/90
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Full name of second joint inventor, if any James W. Young
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Full name of third joint inventor, if any
Third Inventor's Signature Date
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Full name of fourth joint inventor, if any
Fourth Inventor's Signature Date
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Citizenship
Post Office Address

1614

0701.027G

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 09/200,541 Art Unit: Not known

Filed: November 25, 1998 Examiner: Not known

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, January 14, 1999.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: January 14, 1999

To: Assistant Commissioner for Patents
Box Non-Fee Amendment
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.121(a)

Dear Sir:

Prior to examination, please amend the application as follows:

In the Title:

Please change "METHOD" TO --FORMULATIONS--.

In the Claims:

Cancel claims 1-12.

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January 14, 1999

Please add the following claims:

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13. A pharmaceutical formulation suitable for administration by inhalation, comprising R(-) albuterol substantially free of S(+) isomer and a pharmaceutically acceptable carrier for administration by inhalation, said carrier comprising a propellant.

14. The formulation as claimed in claim 13, wherein the quantity of R(-) albuterol is greater than approximately 90% by weight of total albuterol in the formulation.

15. The formulation as claimed in claim 14, wherein the quantity of R(-) albuterol is greater than approximately 99% by weight of total albuterol in the formulation.

16. The formulation as claimed in claim 13, wherein the quantity of R(-) albuterol to be administered per dose by inhalation is from approximately 30 mcg to approximately 90 mcg.

17. The formulation as claimed in claim 13, wherein the carrier is a liquid.

18. The formulation as claimed in claim 13, wherein the formulation is a solution.

19. The formulation as claimed in claim 13, wherein the albuterol is in the form of a powder.

20. An inhaler for administering a pharmaceutical formulation by inhalation comprising R(-) albuterol substantially free of S(+) isomer and a pharmaceutically acceptable carrier for administration by inhalation.

21. The inhaler as claimed in claim 20, wherein the carrier comprises a propellant.

22. The inhaler as claimed in claim 20, wherein the quantity of R(-) albuterol is greater than approximately 90% by weight of total albuterol in the formulation.

23. The inhaler as claimed in claim 20, wherein the quantity of R(-) albuterol is greater than approximately 99% by weight of total albuterol in the formulation.

24. The inhaler as claimed in claim 20, wherein the quantity of R(-) albuterol to be administered per dose by inhalation is from approximately 30 mcg to approximately 90 mcg.

25. A nebulizer for administering a pharmaceutical formulation comprising R(-) albuterol substantially free of S(+) isomer and a pharmaceutically acceptable carrier for administering the formulation in nebulized form.

26. The nebulizer as claimed in claim 25, wherein the quantity of R(-) albuterol is greater than approximately 90% by weight of total albuterol in the formulation.

27. The nebulizer as claimed in claim 25, wherein the quantity of R(-) albuterol is greater than approximately 99% by weight of total albuterol in the formulation.

28. The nebulizer as claimed in claim 25, wherein the quantity of R(-) albuterol to be administered per dose is from approximately 30 mcg to approximately 90 mcg.

29. The nebulizer as claimed in claim 25, wherein the carrier is a liquid.

30. The nebulizer as claimed in claim 25, wherein the formulation is a solution.

REMARKS

Claims 1-12 were present in the application as filed. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-30 are therefore pending in this continuation application.

The present application is a continuation of US application, serial number 09/063,551 (now US patent 5,844,002). By a chain of copending applications [08/691,604 (now US patent 5,760,090); 08/335,480 (now US patent 5,547,994); 08/163,581 (now US patent 5,362,755); and 07/896,725 (abandoned)] this application traces its priority to 07/461,262, filed January 5, 1990. Also claiming priority from 08/335,480 (the grandparent of the instant application) was US application serial number 08/551,911, filed October 23, 1995. A Notice of Allowance was received July 25, 1996, in 08/551,911, but the issue fee was not paid because of

two references that came to light after receipt of the Notice. These references were cited (and overcome) in 08/691,604 (now US patent 5,760,090). The claims of the issued patents 5,844,002; 5,760,090; 5,547,994; and 5,362,755 relate to methods for treating asthma. Applicants now seek to obtain the claims to the corresponding pharmaceutical formulations that were allowed July 25, 1996, in 08/551,911.

Application 08/335,480 issued to US patent 5,547,994 on August 20, 1996. One week before issue, on August 13, 1996, two references were brought to the attention of applicants' undersigned representative. These references had just been provided by a potential licensee and had not been considered in the prosecution of the '480 case. Although applicants believed that the references were merely cumulative to the references already of record (a view which was subsequently confirmed by the examiner), they did not wish to have a cloud hanging over the patent. To ensure explicit consideration of the additional references, applicants immediately filed a Petition to Withdraw from Issue so that the references could be considered. The Petition to Withdraw from Issue was hand carried to the Office of Petitions on August 15, 1996, but it was dismissed because there was insufficient time to withdraw the patent. The filing of the 08/691,604 application and the abandonment of the 08/551,911 application were the results of this process.

The first of the two references not before the examiner when the '911 (formulations) application was allowed was UK patent 1,298,494. It discloses that R(-) albuterol is 50 times more potent than S(+) albuterol in antagonizing acetyl choline-induced

bronchoconstriction in the guinea pig (page 1, column 2, line 68-74). The second new reference, German Patent 2,128,258, which corresponds to UK patent 1,298,494, but which has a slightly differently worded specification, refers to the "high pharmacological activity in particular of the R(-) isomers" and discloses without further quantification that R(-) albuterol "functions as an antagonist of the increased bronchial resistance which is caused in anesthetized guinea pigs as a consequence of acetyl choline."

Applicants' reference CB [Brittain *et al.* Brit. J. Pharmacol. 48, 144-147 (1973)], which was discussed extensively during prosecution of the '911 application and its parents, disclosed that mean equipotent doses for (-) and (+) albuterol in acetyl choline-induced bronchoconstriction in the guinea pig were 2.93 and 112 respectively. Thus applicants urge that, as in the previous cases in which the examiner concurred, the two references add nothing to the existing record, and the claims that were allowed in the '911 application remain allowable.

In order that the record may be complete in this case, applicants submit herewith a copy of the Declaration under 37 CFR 1.132 of John McCullough. This was a Declaration that was submitted in the '911 case and upon which applicants wish to continue to rely to establish unexpected advantages associated with the use of R-albuterol.

Applicants believe that the claims now pending are in condition for allowance, and favorable consideration is respectfully requested.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: January 14, 1999

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January 14, 1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

DECLARATION UNDER 37 C.F.R. §1.132

I, John R. McCullough, declare that:

1. I reside at 6 Davidson Road, Worcester, Massachusetts, 01605;

2. I earned a B.A. in English with a minor in chemistry from the City University of New York in 1970, and a Ph.D. degree in Pharmacology from the State University of New York Downstate Medical Center in 1980. My primary area of research, both during my Ph.D. studies and subsequently over the ensuing fourteen years has been in cellular electrophysiology and pharmacology. I am presently Senior Director of Pharmacology at Sepracor Inc., Marlborough, Massachusetts. Prior to my employment at Sepracor, I had appointments as (sequentially) Guest Professor at the Laboratorium voor Fysiologie, Katholieke Universiteit Leuven, Leuven, Belgium; Research Associate at Northwestern University Medical Center, Chicago, Illinois; Guest Scientist at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany; Senior Scientist at CIBA-Geigy Corp., Pharmaceuticals Division, Summit, New Jersey; and Senior Research Investigator at the Bristol-Myers Squibb Institute for Medical Research, Princeton, New Jersey; I have also been an Adjunct Assistant Professor of Physiology and Biophysics at New York University Medical Center in New York, New York;

decreases in Ca^{2+} are associated with relaxation. Thus, any observed increase in Ca^{2+} induced by a test substance reflects an enhanced predisposition to contraction (hyperreactivity).

The effects of S- and R-Albuterol on intracellular calcium were measured in individual cells from bovine trachea loaded with fura 2 according to the method of Yamaguchi et al [Am. J. Physiol. 268, C771-C779 (1995)] The concentration of Ca^{2+} in a single cell was determined from the ratio of fluorescence emissions resulting from excitation by alternating pulses of 337 and 380 nm light. Individual cells were maintained at 37° C on a heated stage of a Nikon inverted microscope. The microscope was used to image the cells, expose cells to ultraviolet light, and to capture the resulting fluorescence emissions. All drugs were dissolved in physiological salt solution containing 2.5 mM Ca^{2+}. Under these conditions, resting basal levels of Ca^{2+} in the isolated smooth muscle cells average 100-200 nM.

MATERIALS AND METHODS

Single-cell preparation. Tracheal smooth muscle cells were dispersed from strips (0.5 x 5 mm) of bovine trachealis muscle weighing 0.2 g total. The enzyme dispersal was done in 2.5 mL of nominally calcium-free physiological salt solution (PSS) containing collagenase (4 mg, Boehringer-Mannheim) and elastase (3 mg, Boehringer-Mannheim) for 15-25 minutes, yielding cells with consistent levels of basal $[Ca^{2+}]$. The dispersed cells were recovered in low Ca^{2+} (0.1 mM) PSS, loaded with either 0.5 or 10μM fura 2 acetoxymethyl ester (AM) for 30 min at 30-32°C, and then introduced into a heated superfusion chamber (volume ~ 150

μL) that had a bottom cover glass. After adherance of the cells to the glass, PSS containing normal Ca^{2+} (2.3 mM, 37° C) superfused the chamber.

Fluorescent measurement. Cells loaded with fura 2-AM were excited with computer-controlled 337- and 380-nm ultraviolet light generated by a nitrogen laser and a nitrogen laser-pumped dye laser, respectively (Laser Science, Newton, MA). Each laser alternately fired short laser pulses (3 ns) at 30 Hz. These alternating pulses of light were guided by a bifurcated quartz fiber to the epiport of the microscope, where the light intensity was reduced by 90-95% with a neutral density fiber and then focused on cells through a Nikon x 40 objective lens. The fluorescent signals emitted by cells were passed through the objective to a 455-nm dichroic mirror and 475-nm barrier filter (Omega Optics, Brattleborough, VT) and captured by a Philips-based frame transfer charge coupled device (CCD) camera made by CCTV (New York, NY) or Philips Components (Slatersville, RI). The analog video signals from the camera were digitized and stored in a stand-alone imaging device (Recognition Technology, Westborough, MA). With the vertical blanking signals of the CCD camera serving as a master clock, digital outputs from the device were fed into the computer through the digital input-output board.

To measure the concentration of Ca^{2+}, background levels of light were subtracted before data acquisition, and then an area (up to 11 x 11 pixels) away from the nucleus was selected over each cell. The gray levels of fluorescence emissions stimulated by alternating pulses of 337- and 380-nm light were recorded, and

their ratios were plotted in real time for a period of 9 min. Intracellular [Ca^{2+}] was calculated using an equilibrium dissociation constant of 386 nM, a value previously determined in bovine airway smooth muscle cells to represent Ca^{2+} binding to fura 2 in situ.

RESULTS

Acute exposure of the airway smooth muscle cells to the enantiomers of albuterol had opposite effects on basal Ca^{2+} levels: R-albuterol decreased basal levels of Ca^{2+} and S-albuterol increased them. As shown in the attached Figures 1 and 2, these effects were concentration dependent. The threshold for decrease in Ca^{2+} by R-albuterol was 5×10^{-8} M while the threshold for S-albuterol-induced increase in Ca^{2+} was 10^{-11} M. Increased Ca^{2+} results in contraction, while decreases in Ca^{2+} are associated with relaxation. Thus, the increase in Ca^{2+} induced by S-albuterol would predispose cells to contract, and in approximately 25% of the cells exposed to high concentrations of S-albuterol ($\geq 10^{-6}$ M) spontaneous calcium oscillations accompanied by spontaneous cell-shortening were observed. No calcium oscillations or contractions were observed with R-albuterol.

When exposed to a spasmogen such as carbachol, two phases of increased Ca^{2+} are observed: an initial phase involving a large transient increase and a second phase involving a sustained but lesser increase. As demonstrated in Figure 3, R-albuterol reduced both phases of carbachol-induced calcium mobilization, while S-albuterol enhanced both phases.

CONCLUSIONS

The changes in calcium handling observed in the experiments above represent a potential mechanism for bronchial hyperactivity following acute administration of S-albuterol, and further support the conclusion reached by Dr. Dean A. Handley in his Declaration Under 37 CFR 1.132 of June 7, 1995, already of record in the instant patent application. The person of skill in the art would conclude from these experiments that the use of pure R-albuterol for bronchodilation would avoid airway hyperreactivity associated with acute administration of racemic albuterol.

6. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 22nd day of January, 1996.

John R. McCullough

FIGURE 1

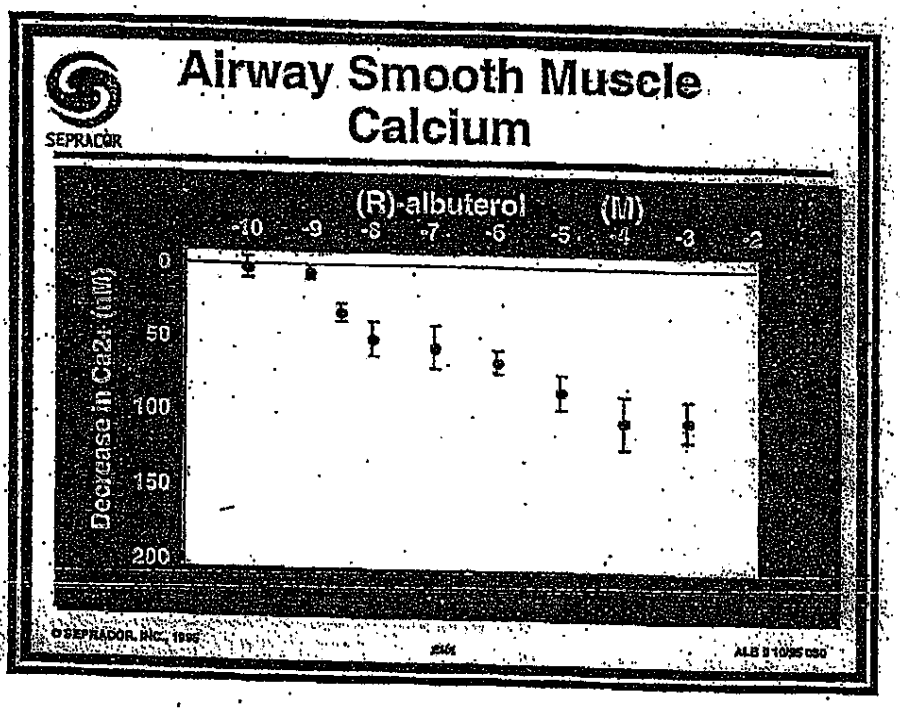

Airway Smooth Muscle
Calcium
SEPRACOR
(R)-albuterol (M)
-10 -9 -8 -7 -6 -5 -4 -3 -2
0
50
100
150
200
Decrease in cell [Ca++] (nM)

FIGURE 2

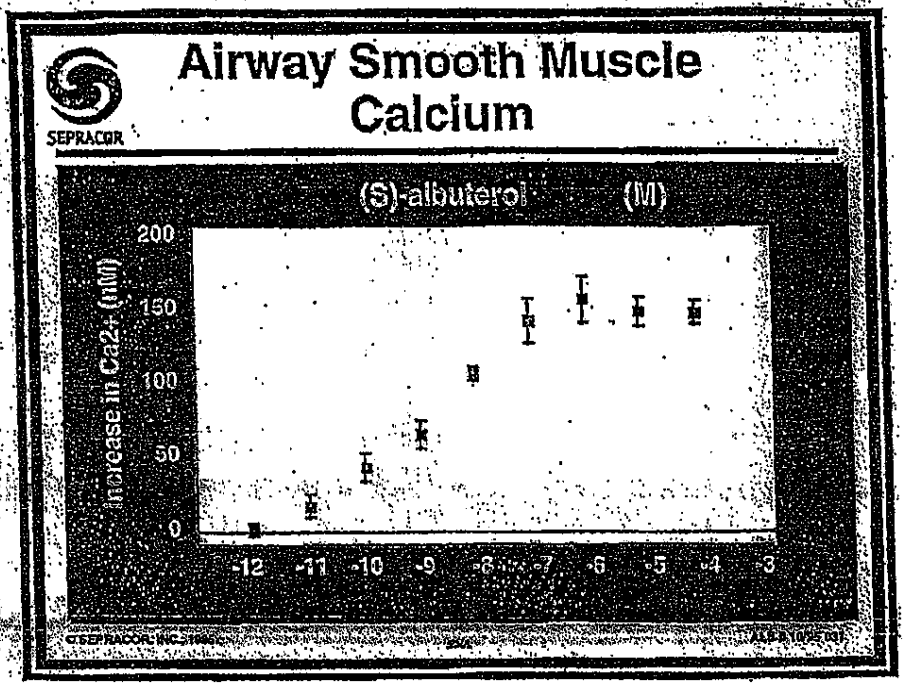
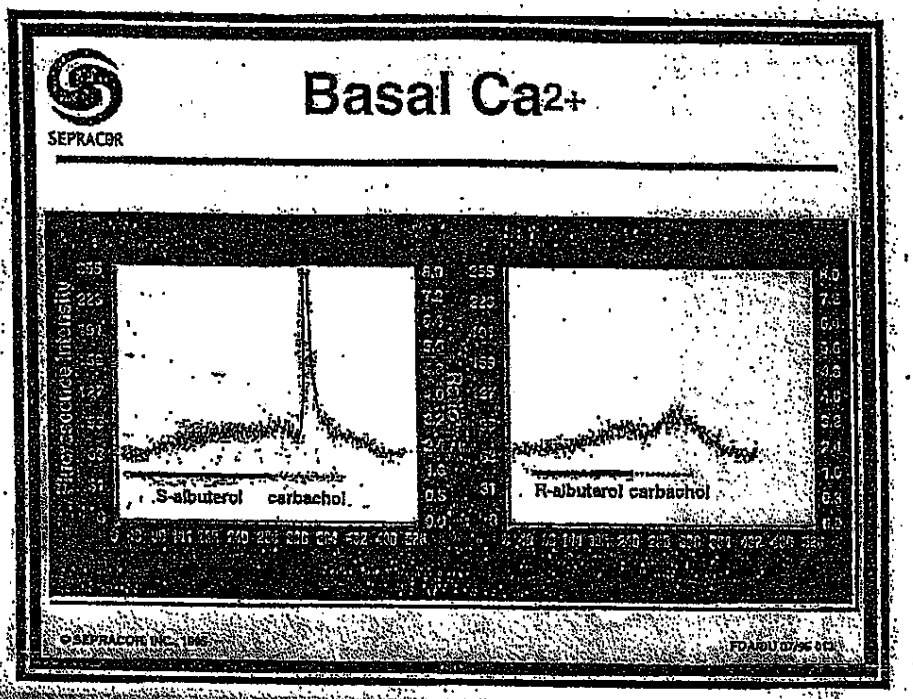

Airway Smooth Muscle Calcium
SEPRACOR
(S)-albuterol (M)
Increase in Ca2+ (nM)
200
150
100
50
0
-12
-11
-10
-9
-8
-7
-6
-5
-4
-3

FIGURE 3


Basal Ca2+
SEPRACOR
S-albuterol carbachol
R-albuterol carbachol

Docket No. 0701.027G

Applicant(s): Barberich et al.

Serial No. 09/200,541 Group Art Unit: Not known

Filed: November 25, 1998 Examiner: Not known

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Assistant Commissioner for Patents
Washington, D.C. 20231

STATEMENT OF RELEVANCE FOR INFORMATION DISCLOSED BY APPLICANT

Sir:

The following Statement of Relevance is submitted in regard to reference BC on the Form 1449 submitted herewith.

Document Designation	Relevance
BC	German Patent 2128258 discloses a process for the preparation of the optical enantiomers of albuterol and in particular the R(-) enantiomer in the form of its acetate methanol solvate. The patent states (column 3, line 30-33) "this purity and the high pharmacological activity in particular of the R(-) isomers are especially useful for the inclusion as active ingredient in medicaments." and (column 3, line 60-64) "the R(-) isomer of the compound of formula I functions as an antagonist of the increased bronchial resistance which is caused in anesthetized guinea pigs as a consequence of acetyl choline (Konzett-Rössler preparation)." The patent describes the synthesis of R(-) and S(-) albuterol and the preparation of tablets and aerosols.

A full text copy of the art cited was submitted, together with Form 1449, on August 23, 1996. It is respectfully requested that this art be considered by the Examiner in the above-entitled application and made of record therein.

Respectfully submitted,

January 14, 1999
Date

Philip E. Hansen
Registration No. 32,700

F:\USERS\RFP\SEPRACOR\07010270.SOR
January 14, 1999

Sheet 1 of 1

INFORMATION DISCLOSURES CITATION	Docket No. 0701.027g	Serial No. 09/200,541
	Applicant: Barberich et al.	
	Filing Date:	Group: 1614

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	Date	Country	Class	Subclass	Translation Yes	Translation No
D	BB	1298494	1972	United Kingdom			X	
E	BC	DE2128258	1983	Germany				X

Other Documents (including Author, Title, Date, pertinent public. etc.)

Examiner [signature] Date Considered 9/11/98

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/200,541	11/25/98	BARBERICH	T 0701.276

HM12/0917

HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

EXAMINER	
HENLEY III, R.	
ART UNIT	PAPER NUMBER
1614	4

DATE MAILED: 09/17/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95) 1- File Copy

DLEV011584

Office Action Summary

Application No.	Applicant(s)
09/200,541	Timothy J. Barberich, et al.
Examiner	**Group Art Unit**
Ray Henley	1614

☐ Responsive to communication(s) filed on _____

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 13-30 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 13-30 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

CLAIMS 13-30 ARE PRESENTED FOR EXAMINATION

Applicants' amendment and Information Disclosure Statement filed January 19, 1999 have been received and entered into the application. Accordingly, claims 1-12 have been canceled and claims 13-30 have been added. Also, as reflected by the attached, completed copy of form PTO-1449, the cited references have been considered.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-15, 17, 18 and 20-23 rejected under 35 U.S.C. 102(b) as being anticipated by Middlemiss (GB 1,298,494). See page 2, column 1, lines 6, 8-13, 16-27 and 38-41 and page 3, columns 1-2, Examples 3-5 where inhalants containing (R-) albuterol and a propellant in liquid form are taught

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Middlemiss, as above.

The differences between the above and applicants' claimed subject matter lies in that Middlemiss fails to highlight:

(1) powdered forms for inhalation or a nebulizer dosage form; and

(2) dosages of from 30 mcg. to 90 mcg.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(1) Middlemiss teaches "forms suitable for inhalation" (page 2, lines 26-27) in general and thus would have suggested to the skilled artisan those known in the art such as nebulizers or powdered forms for inhalation which were readily available; and

(2) the determination of the optimum dosage amount to employ would have been a matter well within the purview of the skilled artisan and would have been expected to vary depending

upon the size, weight and/or age of the patient as well as the severity of the condition being treated.

Accordingly, for the above reasons, the claims are deemed to be properly rejected and none of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Henley whose telephone number is (703) 308-4652.

RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1600

Henley; rjh
September 11, 1999

Sheet 1 of 1

INFORMATION DISCLOSURE CITATION	Docket No. 0701.Q27D	Serial No.
	Applicant: Barberich et al.	
	Filing Date:	Group:

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	Date	Country	Class	Subclass	Translation	
							Yes	No
	BA	2 255 503	1992	UK			X	
	BC	DE2128258	1983	Germany				X
	BD	1298494	1971	UK			X	

Other Documents (including Author, Title, Date, pertinant public. etc.)

	CA	Tan et al. "Stereoselective Disposition of Salbutamol Enantiomers..." Clin. Chem. 33, 1026 (1987)
	GB	Brittain et al. "Some observations on the β-adrenoceptor agonist..." Br. J. Pharmac. 48, 144-147 (1973)
	CC	Hartley et al. "Absolute Configuration of the Optical Isomers of Salbutamol" J. Med. Chem. 12, 995 (1971)
	CD	Hawkins et al. "Relative Potency of (-)- and (±)-Salbutamol on Guinea Pig..." J. Med. Chem. 16, 856-857 (1973)
	CE	Buckner et al. "Studies on the Effects of Enantiomers of Soterenol, Trimetoquinol..." J. Pharm. Exp. Ther. 189, 616-625 (1974)
	CF	Passowicz-Muszynska E. "Effect on beta adrenergic receptors of tachyphylaxis..." Index Medicus 91:164287
	CG	Pauwels "Effect of corticosteroids on the action of sympathomimetics" Index Medicus 86:051970
	CH	Chapman et al. "An anomalous effect of salbutamol in sensitised guinea pigs" Brit. J. Pharmacol 99, 66P (1990)
	CI	Morley et al. "Effects of (+) and racemic salbutamol on airway responses in the guinea pig" Brit. J. Pharmacol. 104, 295P (1991)
	CJ	Chapman et al. "Racemic mixtures at root of worsening symptoms? Active enantiomers..." TIPS 13, 231-232 (1992)
	CK	Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol,..." Chem. Abstr. 89: 123259m (1978)

Examiner	Date Considered

45

HESLIN & ROTHENBERG, P.C.

ROBERT E. HESLIN*
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INTELLECTUAL PROPERTY LAW
PATENTS TRADEMARKS COPYRIGHTS

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DANIEL H. BEATY

September 3, 1999

No. of Pages Transmitted: 3

Fax No.: (703) 308-7751

Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: Application Processing Division's
Customer Correction Branch

Re: Patent Application
Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL
Serial No.: 09/200,541
Filing Date: 11/25/98
Attorney Docket No.: 0701.027G

Dear Sir:

Attached is a copy of a recently received filing receipt in which the following errors appear in the total number of independent claims, filing receipt received and attorney docket number.

The total number of independent claims "2", should read --3--.

The total amount of the filing fee "$760.00", should read --$380.00--.

The attorney docket number "0701.27G", should read --0701.027G--.

F:\USERS\RFP\SEPRACOR\027G.COR

Kindly make the appropriate corrections and return a corrected filing receipt.

Very truly yours,

HESLIN & ROTHENBERG, P.C.

Philip E. Hanson

PEH/rfj
Enc.

F:\USERS\RFF\SEPRACOR\027G.COR
September 3, 1999

SEP. -03' 99(FRI) 13:23 HESLIN & ROTHENBERG TEL:518 452 5579 P.003

PTO-103X (Rev. 6-89)

FILING RECEIPT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
09/200,541	11/25/98	1614	$760.00	0701.27G	0	12	2

HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts of Application" ("Missing Parts Notice") in this application, please submit any corrections to this Filing Receipt with your reply to the "Missing Parts Notice." When the PTO processes the reply to the "Missing Parts Notice," the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s) TIMOTHY J. BARBERICH, CONCORD, MA; JAMES W. YOUNG, STILL RIVER, MA.

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 01/14/99
TITLE
METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

PRELIMINARY CLASS: 514

RECEIVED
JUL 22 1999
HESLIN & ROTHENBERG

DATA ENTRY BY: LOVER, ANTHONY TEAM: 08 DATE: 07/20/99

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/200,541	11/25/98	BARBERICH T	0701.027G

HM12/0426

HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

EXAMINER	
HENLEY III,R	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	NAMED APPLICANT	ATTORNEY DOCKET NO.
09/[illegible]541	11/[illegible]/98	BARBERIS	11011.0278

HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

HM22/0426

HENLEY III,R

ART UNIT 1614 PAPER NUMBER

DATE MAILED: 6/26/00

NOTICE OF ABANDONMENT

This application is abandoned in view of:

☒ Applicant's failure to timely file a proper response to the Office letter mailed on Sep. 17, 1999.

☐ A response (with a Certificate of Mailing or Transmission of _____) was received on _____, which is after the expiration of the period for response (including a total extension of time of ___ month(s)) which expired on _____.

☐ A proposed response was received on _____, but it does not constitute a proper response to the final rejection.

(A proper response to a final rejection consists only of: a timely filed amendment which places the application in condition for allowance; a Notice of Appeal; or the filing of a continuing application under 37 CFR 1.62 (FWC).

☒ No response has been received.

☐ Applicant's failure to timely pay the required issue fee within the statutory period of three months from the mailing date of the Notice of Allowance.

☐ The issue fee (with a Certificate of Mailing or Transmission of _____) was received on _____

☐ The submitted issue fee of $_____ is insufficient. The issue fee required by 37 CFR 1.18 is $_____.

☐ The issue fee has not been received.

☐ Applicant's failure to timely file new formal drawings as required in the Notice of Allowability.

☐ Proposed new formal drawings (with a Certificate of Mailing or Transmission of _____) were received on _____.

☐ The proposed new formal drawings filed _____ are not acceptable.

☐ No proposed new formal drawings have been received.

☐ The express abandonment under 37 CFR 1.62(g) in favor of the FWC application filed on _____

☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a) upon the filing of a continuing application.

☐ The decision by the Board of Patent Appeals and Interferences rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

☐ The reason(s) below:

RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1600

FORM PTO-1432 (REV. 10-95)

Interview Summary

Application No.	Applicant(s)
09/200,541	Timothy J. Barberich et al.
Examiner	**Group Art Unit**
Ray Henley	1614

All participants (applicant, applicant's representative, PTO personnel):

(1) *Ray Henley* (3) _____

(2) *Philip Hansen* (4) _____

Date of Interview *Apr 24, 2000*

Type: [X] Telephonic [ ] Personal (copy is given to [ ] applicant [ ] applicant's representative).

Exhibit shown or demonstration conducted: [ ] Yes [X] No. If yes, brief description:

Agreement [ ] was reached. [X] was not reached.

Claim(s) discussed: *None*

Identification of prior art discussed:
None

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Application is abandoned.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. [X] It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. [ ] Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1600

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

U. S. Patent and Trademark Office
PTO-413 (Rev. 10-95) Interview Summary Paper No. 6

PTO/SB/58 (11-96)
Approved for use through 10/31/98. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

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TECH CENTER 1600/2900

In re Application of		
Application Number	Filed	
09/200,541	Nov 25, 1998	
Group Art Unit	Examiner	

Paper No. _____

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

___ (A) referred to in United States Patent Number 6083993, column _____,

___ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____,

___ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or

___ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

_____

_____

_____

_____ Feb 20, 2001
Signature Date

Duff Mullaney
Typed or printed name

FOR PTO USE ONLY
Approved by: _____ (Initials)
Unit: _____

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

PTO/SB/36 (11-00)
Approved for use through 10/31/02. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

RECEIVED
DEC 1 8 2001
File Information Unit

In re Application of	
Bar-Berich et al.	
Application Number	**Filed**
09/200,541	11-25-98
Group Art Unit	**Examiner**

Paper No. #7

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In re Application of	
Application Number: 09/200,541	Filed: 11-25-98
Art Unit	Examiner

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In re Application of: Barbieri et al

Application Number: 09/200,541 Filed: 11-25-98

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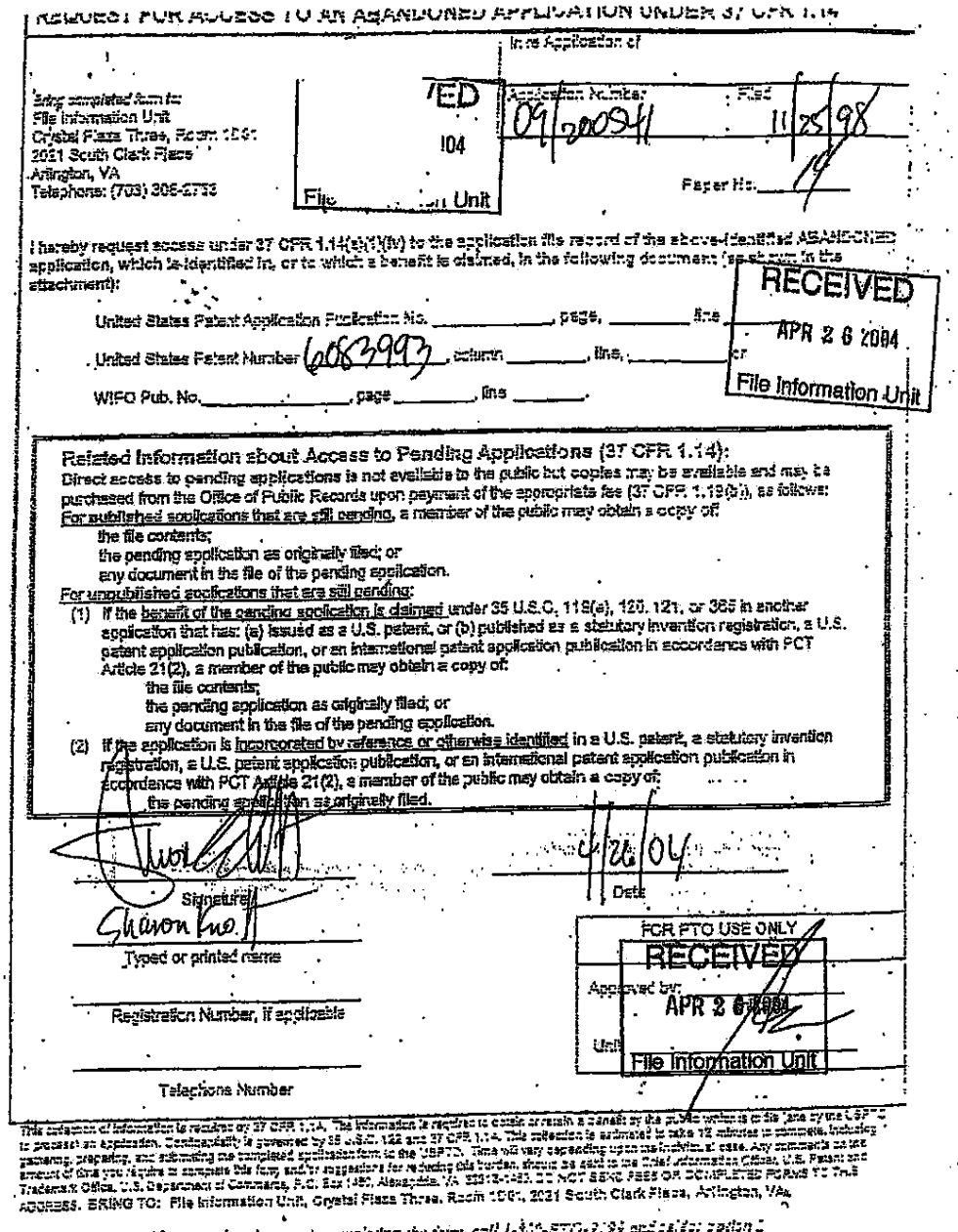

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Steven L. Oley
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EXHIBIT 21

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EXHIBIT 22

National Asthma Education Program

Expert Panel Report

Guidelines for the Diagnosis and Management of Asthma

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

National Asthma Education Program

Expert Panel Report

Guidelines for the Diagnosis and Management of Asthma

National Asthma Education Program
Office of Prevention, Education, and Control
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland 20892

Publication No. 91-3042
August 1991

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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List of Figures

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Foreword

Asthma morbidity and mortality are on the rise. From 1980 to 1987, the prevalence rate of asthma in the United States increased 29 percent, and death rates for asthma as the first-listed diagnosis increased 31 percent. In 1988, asthma-related health care expenditures exceeded $4 billion in the United States. Yet these changes are occurring at a time when scientific advances are improving our understanding of asthma and providing new therapies.

To help all health care professionals bridge the gap between research and practice, the Coordinating Committee of the National Asthma Education Program (NAEP) convened an expert panel. The charge was to develop guidelines to improve the detection and treatment of asthma.

This publication, the first major report on asthma from the NAEP, is likely to have a profound effect on the way asthma is treated. It reflects the current state of knowledge about the underlying causes of asthma and presents detailed recommendations to guide the diagnosis and management of asthma.

In issuing these guidelines, the panel emphasizes that these are general guidelines developed to assist clinician and patient decisions about appropriate asthma care; specific therapeutic regimens must be tailored to individual needs and circumstances. The expert panel's recommendations represent a broad consensus because they are based upon review of the scientific literature, the expert judgement and collective opinion of the panel members, and review and approval by members of the Coordinating Committee of the National Asthma Education Program. However, these guidelines are not to be construed as either an official regulatory document or as a document that has been endorsed by the United States Food and Drug Administration. Furthermore, because research on asthma is a dynamic process, recommendations of the expert panel will be adjusted as scientific research advances.

People with asthma can expect to control their symptoms, prevent asthma episodes, be physically active, and breathe normally. This report presents guidelines to help clinicians and patients meet these goals of asthma care.

People with asthma usually seek care from their primary care physician or nurse, who might then refer them to an asthma specialist. This report, therefore, is designed principally to provide these clinicians with new insights into asthma management. It is hoped that the report will also be of use to others involved in asthma care, including, among others, respiratory care therapists, health educators, social workers, and psychologists—and, of course, the asthma patient.

On behalf of the National Asthma Education Program Coordinating Committee and the National Heart, Lung, and Blood Institute, I would like to acknowledge the superb work of the expert panel and the outstanding leadership of its chair, Dr. Albert L. Sheffer. The development of this report was a challenging task, one that Dr. Sheffer and the panel members carried out with vigor, dedication, and a commitment to excellence.

Claude Lenfant, M.D., Director
National Heart, Lung, and Blood Institute
Chairman, National Asthma Education Program
Coordinating Committee

Preface

It was an honor for the expert panel to accept the task of developing guidelines for the diagnosis and management of asthma. With appropriate therapy, patients with asthma can expect to control their symptoms, prevent most acute asthma exacerbations, maintain the activity levels they desire, and attain near normal lung function.

Asthma is a chronic disease with acute exacerbations and, therefore, requires continuous medical care. Treatment requires four critical components: patient education that fosters a partnership among the patient, family, and clinician; preventive and environmental control measures to avoid factors that induce or trigger asthma exacerbations, including consideration of immunomodulation; comprehensive pharmacologic therapy designed to reverse and, preferably, prevent the airway inflammation characteristic of asthma, as well as to treat bronchospasm; and the use of objective measures to assess the severity of asthma and to monitor the course of therapy.

This report of the expert panel is organized into eight chapters that elaborate on each of these elements of care. The other chapters delineate considerations to take into account when adapting recommendations to special patient circumstances. The expert panel developed its recommendations not as prescriptions for individual treatment but rather as guidelines for use by the patient and clinician as they select a therapeutic plan.

Many health professionals, in addition to the clinician, are involved in asthma care. Through this report we hope to encourage an informed collaboration among all health professionals and asthma patients leading to the best possible care.

Asthma is a chronic disease and its treatment requires four components: patient education, environmental control, comprehensive pharmacologic therapy, and objective measures to assess severity and monitor the course of therapy.

The report is the result of an extensive development, review, and approval process. The panel wishes to thank the following individuals who served as consultants to the panel and reviewed an initial draft: Homer Boushey, Jr., M.D., University of California, San Francisco; William Kelly, Pharm.D., University of New Mexico; E. Regis McFadden, Jr., M.D., Case Western Reserve University and University Hospitals of Cleveland; Guillermo Mendoza, M.D., Hawthorne Community Medical Group; Richard Nicklas, M.D., George Washington University; and Charles Reed, M.D., Mayo Clinic. All members of the NAEP Coordinating Committee participated in three cycles of review and revisions. The final report was approved at the February 5, 1991, meeting of the NAEP Coordinating Committee. I am grateful to all for contributing to the effort so astutely and in such a timely manner.

It is rewarding to note that the recommendations in the report represent the collective opinion of the panel. The recommendations are based on the expert panel discussions, held over the course of five meetings, which included review of the scientific literature available before January 1, 1991, and the expert judgement of panel members. Further review by the community at large, combined with continuing medical advances in the understanding of asthma, will be used by the National Asthma Education Program to generate appropriate and timely revisions of this document.

Albert L. Sheffer

Albert L. Sheffer, M.D.
Chair
Expert Panel on the Management of Asthma

1
Definition and Diagnosis

Thirty years after the first formal attempt by an expert study group to define asthma,[1] a widely accepted definition remains elusive. The clinician, physiologist, immunologist, and pathologist all have different perspectives of asthma, and these perspectives are difficult to merge into a comprehensive definition sufficiently specific to exclude other disease entities that may share one or more of the characteristics of asthma. Furthermore, as a disorder that encompasses virtually the entire spectrum of life, asthma has certain age-specific characteristics and differential diagnostic problems. In light of our current knowledge, the generally agreed-on working definition of asthma recognizes that:[2-4]

> Asthma is a lung disease with the following characteristics: (1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; (2) airway inflammation; and (3) increased airway responsiveness to a variety of stimuli.

Current statistics on asthma illustrate the significance of asthma in public health and asthma's impact on the health care system.

Prevalence. An estimated 10 million persons in the United States have asthma. In the general population, asthma prevalence rates increased 29 percent from 1980 to 1987 (see Figure 1-1).

Outpatient visits. Asthma is generally treated in outpatient settings. In 1985, there were 6.5 million visits for asthma as a first-listed diagnosis (1 percent of the total) among 640 million total estimated ambulatory care visits in the National Ambulatory Medical Care Survey.[5]

Hospitalizations. From 1980 to 1987, the hospital discharge rate for asthma as the first-listed diagnosis increased 6 percent. However, from 1970 to 1987, hospital discharge rates for asthma increased nearly threefold. African Americans were more than twice as likely as Caucasians to be hospitalized.[6]

Mortality. From 1980 to 1987, the death rate from asthma increased 31 percent (2,891 persons died in 1980; 4,360 persons died in 1987).[6] Chapter 3, Asthma Mortality, includes discussion of these data.

Underdiagnosis of asthma is a frequent problem. For children, wheezing with respiratory infections is often asthma rather than wheezy bronchitis or pneumonia. For both children and adults, recurrent episodes of cough and wheezing are almost always due to asthma.

All health care providers have a fundamental role in improving the diagnosis of asthma and helping prevent morbidity and mortality from asthma through appropriate management techniques. This chapter will assist diagnosis; the following chapters will discuss recommendations for the management of asthma.

Pathophysiology

The development of airway obstruction is responsible for the clinical manifestations of asthma.

In mild asthma, there may be no obvious clinical evidence of airflow obstruction or any changes detectable during routine pulmonary function testing.[7] However, more sensitive laboratory assessment may reveal airway hyperresponsiveness and abnormalities in peripheral airway function.[7-9]

In moderate and severe asthma, bronchial reactivity increases, and evidence of airflow obstruction will be apparent upon physical examination and during pulmonary function testing (spirometry and peak expiratory flow rate measurements).[4,7]

There is considerable lability in the responsiveness of asthmatic airways. Airway narrowing may worsen gradually and persist despite therapy, but it can also develop abruptly and produce acute respiratory insufficiency.

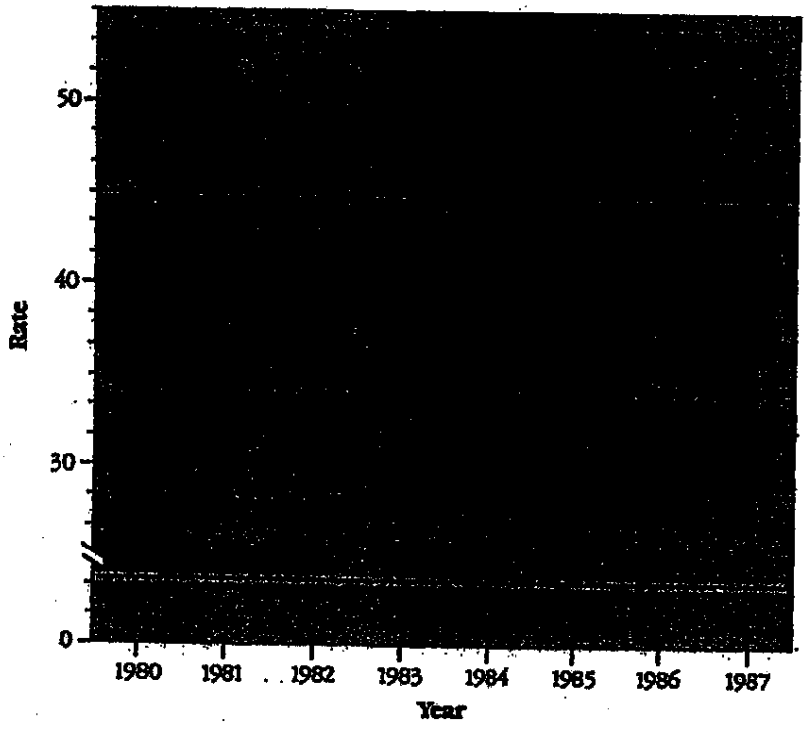
The changes associated with airway obstruction in asthma are thought to be initiated by the inflammatory events in the airways.[6] The airways of asthma patients are infiltrated by inflammatory cells,[7] have epithelial disruption,[8] and show evidence of mucosal edema. Airway inflammation is also thought to be a primary mechanism responsible for airway hyperresponsiveness in asthma.[9]

Airway Hyperresponsiveness

Asthma is characterized by airway hyperresponsiveness, a condition manifested by an exaggerated bronchoconstrictor response to many physical changes and chemical and pharmacologic agents.[2] Asthma patients develop such clinical symptoms as wheezing and dyspnea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Airway hyperresponsiveness also appears to be important in the pathogenesis of asthma, as it is ubiquitous in the disease.[10] Furthermore, the level of airway responsiveness usually correlates with the clinical severity of asthma and medication requirements.[11]

The level of airway hyperresponsiveness can be measured in the laboratory by standard inhalation challenge testing with methacholine or histamine as well as after exposure to such nonpharmacologic stimuli as

Figure 1-1
Prevalence Rates of Asthma, per 1,000 Persons, by Age and Year—National Health Interview Survey United States, 1980-87



Source: Centers for Disease Control. Asthma—United States, 1980-87. Center for Chronic Disease Prevention and Health Promotion, Office of Surveillance and Analysis, Chronic Disease Surveillance Branch.

hyperventilation with cold dry air, inhalation of hypo- or hypertonic aerosols, or after exercise.[3] In addition, fluctuations in morning (a.m.) and evening (p.m.) peak expiratory flow rates (PEFR) appear to reflect airway hyperresponsiveness and serve as a measure of airway hyperresponsiveness in asthma.[12]

Several mechanisms have been proposed to explain airway hyperresponsiveness in asthma, including airway inflammation, abnormalities in bronchial epithelial integrity, alterations in autonomic neural control of airways, changes in intrinsic bronchial smooth muscle function, and baseline airflow obstruction.[2,6,7,9,13]

The mechanisms contributing to airway inflammation in asthma are multiple and involve a number of different inflammatory cells. It is unlikely that asthma is caused by either a single cell or a single inflammatory mediator. Asthma results from complex interactions among inflammatory cells, mediators, and the cells and tissues resident in the airways.[14,15] An initial trigger in asthma may be the release of inflammatory mediators from bronchial mast cells, macrophages, and epithelial cells.[7,16] These substances cause the directed migration and activation of other inflammatory cells (eosinophils and neutrophils), which then produce alterations in epithelial integrity, abnormalities in autonomic neural control of airway tone, changes in mucociliary function, and increased airway smooth muscle responsiveness (see Figure 1-2).[6,17]

Airway Inflammation

Although each of the mechanisms listed above may contribute to the development of airway hyperresponsiveness, the evidence suggesting the presence of airway inflammation in all asthma subjects indicates that airway inflammation is a key factor. Morphological studies show that bronchial infiltration with inflammatory cells is most evident in severe disease but can also be found in mild asthma.[7,8,13,14] There is also evidence to suggest that altered cellular responses and increased levels of inflammatory mediators are associated with asthma and airway hyperresponsiveness.[15,17] Furthermore, therapeutic interventions that reduce bronchial inflammation in asthma patients appear to decrease the degree of airway hyperresponsiveness.[7,18]

Epithelial Injury

One consequence of inflammation is epithelial injury. Morphologic studies have shown that asthma is associated with epithelial injury.[7,8] These changes range from minor disruption of the epithelium with loss of ciliated cells to complete denudation of the epithelium. These structural changes in the epithelial barrier can lead to increased permeability to inhaled allergens,

irritants, and inflammatory mediators. In addition, transudation of fluids and reduced clearance of inflammatory substances and respiratory secretions occur with disruption of epithelium mucociliary mechanisms. The epithelium also participates in mediator release and metabolism.

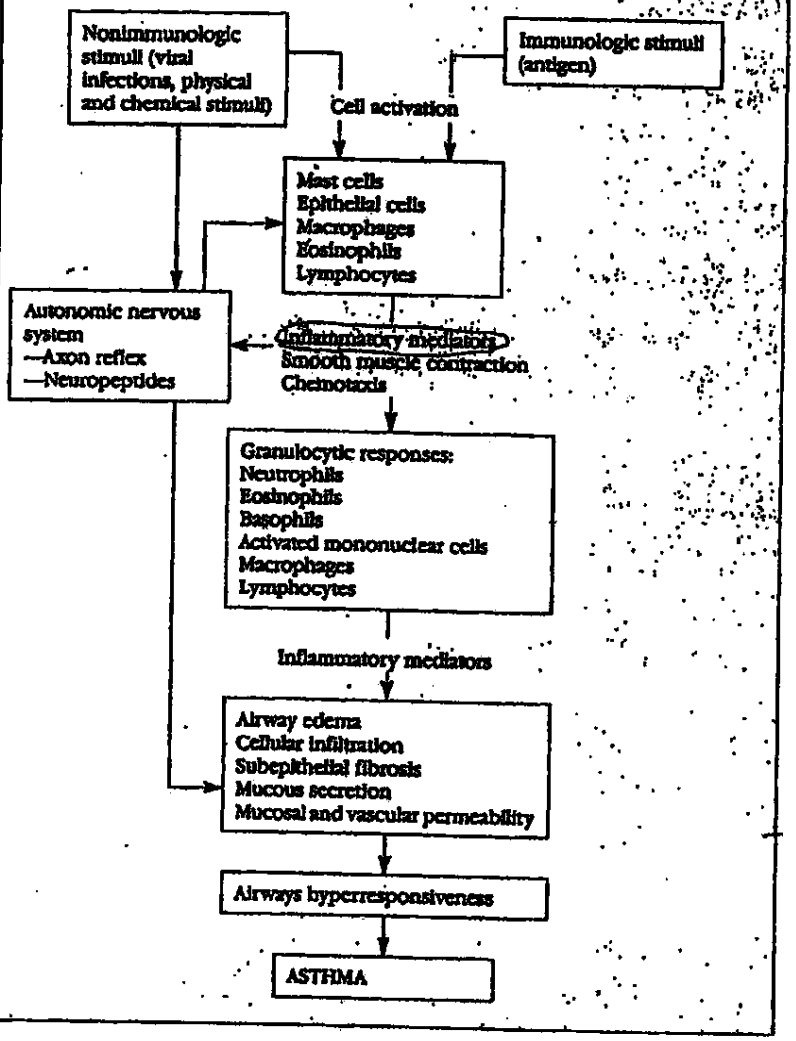
Neural Mechanisms

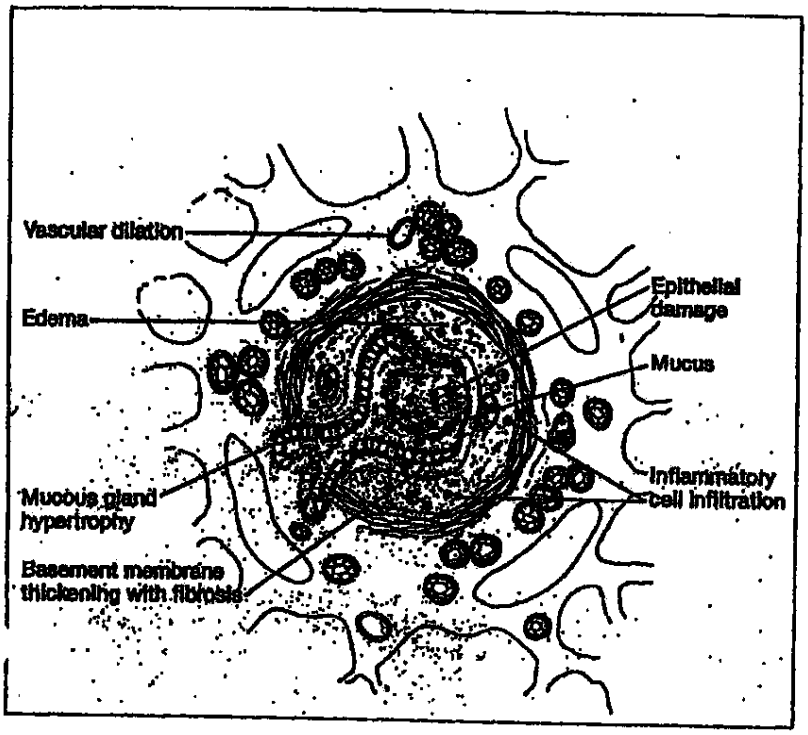
Neural regulation of the human airway is complex.[26,28] The airways of asthma patients are characterized by increased responsiveness to cholinergic substances, which suggests that there are changes in the parasympathetic control of airway function in these individuals. Elevated parasympathetic tone and reflex bronchoconstriction may occur as a consequence of increases in cholinergic sensitivity or changes in muscarinic receptor function. However, recent evidence suggests that alterations in these parasympathetic control mechanisms are only partially responsible for bronchospasm produced by inhaled irritants.

Intrinsic Airway Smooth Muscle Function

Although histological sections of the airways from asthma patients often show bronchial smooth muscle hypertrophy (see Figure 1-3), the importance of these changes in the development of increased airway responsiveness has not been established.[3] Recent in vitro studies of bronchial smooth muscle obtained from asthma patients show a relationship between airway smooth muscle function and the degree of in vivo bronchial responsiveness. However, it is still believed that other exogenous factors also influence airway smooth muscle function in asthma.

Figure 1-2
Proposed Pathways in the Pathogenesis of Bronchial Inflammation and Airway Hyperresponsiveness





Airflow Obstruction

Airflow obstruction is determined by the diameter of the airway lumen, which can be influenced by a number of factors, including edema of the bronchial wall, mucus production, airway smooth muscle contraction, and hypertrophy (see Figure 1-3). However, although airflow obstruction may contribute to bronchial hyperresponsiveness, it is not the primary cause, because bronchial hyperresponsiveness is found in asymptomatic asthma patients with normal pulmonary function.[3]

Pathophysiology of Exacerbations of Asthma

Physiologic Changes

Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms. Exacerbations are characterized by decreases in expiratory airflow. Bronchial smooth muscle contraction is a primary obstructive abnormality in asthma. Other physiologic changes, however, contribute to the following clinical findings characteristic of acute exacerbation of asthma:

Airways narrow because of bronchospasm, mucosal edema, and mucus plugging. Air is trapped behind occluded or narrowed small airways.

- Functional residual capacity rises, and the asthma patient breathes close to his or her total lung capacity.[1,4,5] This hyperinflation enables asthma patients to keep their airways open, thus permitting gas exchange to occur.
- Patients use accessory muscles of respiration (the sternocleidomastoid muscles) to maintain the lungs in a hyperinflated state.[5]

The use of accessory muscles of respiration and the degree of pulmonary hyperinflation correlate better than dyspnea and wheezing with the severity of an impairment in pulmonary function during an acute asthma exacerbation.[5]

However, to assess the severity of acute asthma objectively, measurements of airflow are critical. Measures of forced expiratory volume at one second (FEV_1) and PEFR reflect expiratory airflow obstruction; the reduction in forced vital capacity (FVC) correlates with the level of hyperinflation of the lungs.

- Hypoxemia occurs during severe asthma exacerbations because of mismatching of ventilation and perfusion (V/Q).[22] Usually, during the early stages of an asthma exacerbation alveolar ventilation is maintained, and arterial CO_2 levels are reduced (hypocapnia). When more severe airflow obstruction causes the FEV_1 or PEFR to be below 25 percent of predicted, there is often alveolar hypoventilation, an increase in arterial CO_2, and occurrence of acute respiratory insufficiency.[22]
- Increased pulmonary vascular resistance may occur as a result of hypoxemia and pulmonary hyperinflation during a severe exacerbation. Acute right axis deviation "p-pulmonale" and a right ventricular strain pattern are sometimes seen in the electrocardiogram during acute exacerbations.[4]

■ Negative pleural pressures become more negative as lung hyperinflation occurs, producing an increased afterload on the left ventricle. These changes in pleural pressure and lung volume are manifested clinically by the development of pulsus paradoxus during severe asthma. This fall in systolic pressure during each inspiration can be detected by feeling the pulse and can be quantified with a blood pressure cuff. The presence of pulsus paradoxus during an acute exacerbation of asthma implies that the FEV_1 is reduced to less than half of the predicted normal FEV_1 for that patient.[4]

Late Asthmatic Reactions

Asthma is a complex interaction of many cell types and airway tissues, and mediators released during later phases of the disease can directly alter airway smooth muscle tone, secretion from submucosal glands, inflammatory cell recruitment, and fluid transudation.

The airway response to inhaled antigens provides a very useful model to evaluate the pathogenesis of asthma and mechanisms of airway hyperresponsiveness.[25] Information obtained from this model also has important therapeutic implications.

Inhalation of an antigen first triggers immediate bronchoconstriction; in about half of subjects with asthma, it also provokes a delayed reaction 4-8 hours later. The late response is characterized by persistent airflow obstruction, airway inflammation, and bronchial hyperresponsiveness.[26] Mast cell degranulation and release of bronchospastic mediators are thought to be important in the immediate response (see Figure 1-2).[16,18] The mast cell participation in the late phase response is less clearly defined. However, it appears likely that mediators released from mast cells attract other inflammatory cells to the airways. Of particular importance is the finding that there are increased numbers of eosinophils in the airways during the late response.[16,17] The eosinophil has the capacity to cause airway injury with mediator release and to alter epithelial function. In addition, other cells found in the airways during the late response (neutrophils, macrophages, basophils, and lymphocytes) are important in this inflammatory process. Lymphocytes and macrophages, for example, can secrete cytokines, which upregulate inflammatory cells; lymphocytes and macrophages also cause growth of mast cells and may activate other cells including eosinophils.[7]

Viral Respiratory Infections and Asthma

Although considerable insight has been gained in the pathogenesis of asthma by studying allergic reactions, viral respiratory infections also provoke and alter asthmatic responses. Viral respiratory illnesses may produce their effect by causing epithelial damage, producing specific Immunoglobulin E (IgE) antibodies directed against respiratory viral antigens and enhancing mediator release. Besides aggravating clinical asthma, viral upper respiratory infections increase airway responsiveness that may persist for weeks beyond the infection.[25]

Therapeutic Implications of Airway Inflammation and Airway Hyperresponsiveness

Whether airway hyperresponsiveness, an abnormality that is fundamental to the pathogenesis of asthma, is present at birth in genetically predisposed individuals or whether it is acquired is a subject of current debate (although it is well known that individuals can develop asthma as a direct result of occupational exposures). However, once present, the fact that airway hyperresponsiveness may be increased and perpetuated by agents that cause airway inflammation has important therapeutic implications, i.e., treatment with anti-inflammatory agents may modify airway hyperresponsiveness, improve asthma symptoms, and reduce the need for frequent use of bronchodilators.[6,28]

Diagnosis of Asthma

The diagnosis of asthma is based on the patient's medical history, physical examination, and laboratory test results. It is important to recognize that patients with asthma are heterogeneous, falling into every age group from infancy to old age, and that they present a spectrum of signs and symptoms that vary in degree of severity from patient to patient, as well as within each patient, over time.

Medical History

Topics to include in the history are:

I. Symptoms
   A. Cough, wheezing, shortness of breath, chest tightness, and sputum production (generally of modest degree).
   B. Conditions known to be associated with asthma, such as rhinitis, sinusitis, nasal polyposis, or atopic dermatitis.

II. Pattern of symptoms
   A. Perennial, seasonal, or perennial with seasonal exacerbation.
   B. Continuous, episodic, or continuous with acute exacerbations.
   C. Onset, duration, and frequency of symptoms (days per week or month).
   D. Day-night (circadian) variation with special reference to nocturnal symptoms.

III. Precipitating and/or aggravating factors
   A. Viral respiratory infections.
   B. Exposure to environmental allergens (pollens, molds, house-dust mite, cockroach, animal danders, or secretory products, e.g., saliva or urine).
   C. Exposure to occupational chemicals or allergens.

D. Environmental change (e.g., moving to a new home, going on a vacation, and/or alterations in workplace, work processes, or materials used).

E. Exposure to irritants, especially tobacco smoke and strong odors, air pollutants (ozone, sulfur oxide, nitrous oxide), occupational chemicals, vapors, gases, and aerosols.

F. Emotional expressions: fear, anger, frustration, crying, hard laughing.

G. Drugs (aspirin, beta blockers, nonsteroidal anti-inflammatory drugs, others).

H. Food additives (sulfites).

I. Changes in weather, exposure to cold air.

J. Exercise.

K. Endocrine factors (e.g., menses, pregnancy, thyroid diseases).

IV. Development of disease
A. Age of onset, age at diagnosis.

B. Progress of disease (better or worse).

C. Previous evaluation, treatment, and response.

D. Present management and response, including plans for managing acute episodes.

V. Profile of typical exacerbation
A. Prodromal signs and symptoms (e.g., itching of skin of the anterior neck, nasal allergy symptoms).

B. Temporal progression.

C. Usual management.

D. Usual outcome.

VI. Living situation
A. Home age, location, cooling and heating (central with oil, electric, gas, or kerosene space heating), wood-burning fireplace.

B. Carpeting over a concrete slab.

C. Humidifier.

D. Description of patient's room with special attention to pillow, bed, floor covering, and dust collectors.

X. E. Animals in home.

F. Exposure to cigarette smoke, direct or sidestream, in home.

VII. Impact of disease
A. Impact on patient.
1. Number of emergency department or urgent care visits and hospitalizations.
2. History of life-threatening acute exacerbation, intubation, or oral steroid therapy.
3. Number of school or work days missed.
4. Limitation of activity, especially sports.
5. History of nocturnal awakening.
6. Effect on growth, development, behavior, school or work achievement, and lifestyle.

B. Impact on family.
1. Disruption of family dynamics, routines, or restriction of activities.
2. Effect on siblings and spouse.
3. Economic impact.

VIII. Assessment of family's and patient's perception of illness
A. Patient, parental, and spousal knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment.

B. Ability of patient and parents or spouse to cope with disease.

C. Level of family support and patient and parents' or spouse's capacity to recognize severity of an exacerbation.

D. Economic resources.

IX. Family history
A. IgE mediated allergy in close relatives.

B. Asthma in close relatives.

Medical history
A. General medical history and history of other allergic disorders (e.g., chronic rhinitis, atopic dermatitis, sinusitis, nasal polyps, gastrointestinal disturbances, adverse reactions to foods, drugs); in children, history of early life injury to the airways (e.g., bronchopulmonary dysplasia, history of pulmonary infiltrates, documented pneumonia, viral bronchiolitis, recurrent croup, symptoms of gastroesophageal reflux, passive exposure to cigarette smoke); in adults, cigarette smoking history.

B. Detailed review of symptoms.

Physical Examination

The physical examination for chronic asthma (see Chapter 8, Management of Acute Exacerbations of Asthma) focuses on the upper respiratory tract, the chest, and the skin. Relevant findings may include:

- Presence of rhinitis and/or sinusitis (e.g., purulent nasal discharge and postnasal drip suggest sinusitis), nasal polyps.
- Evidence of hyperinflation of the lungs, particularly in children (e.g., use of accessory muscles, appearance of hunched shoulders and "pigeon chest").
- Quality of breath sounds. Wheezing is the characteristic breath sound of asthma, but it is not a reliable indication of severity. The intensity of the breath sounds in symptomatic asthma is typically reduced. A prolonged phase of forced expiration is typical of airflow obstruction.
- Flexural eczema.

Laboratory Studies

Spirometry (to document severity of airflow obstruction and to establish acute bronchodilator responsiveness) should be undertaken for all patients in whom the diagnosis of asthma is being considered (see Chapter 2, Objective Measures of Lung Function). This may be performed by primary care physicians or asthma specialists.

Additional studies should be considered in all patients and performed where appropriate. These may include:

- Complete blood count (CBC).
- Chest x-ray. (This can rule out other causes of airway obstruction. A recent x-ray is especially important for children.)
- Sputum examination and stain for eosinophilia. (Sputum eosinophilia are highly characteristic of asthma; neutrophils predominate in bronchitic sputum.)
- Nasal secretion and stain for eosinophils. (Neutrophilic nasal discharge is characteristic of sinusitis.)
- Complete pulmonary function studies, including inspiratory and expiratory flow volume curve. (May reveal the presence of upper airway problems that simulate asthma.)
- Determination of specific IgE antibodies to common inhalant allergens with skin tests or with in vitro test (evaluation of inhalant allergy). Investigation of the role of allergy in the patient's asthma may be useful, given the high prevalence of positive skin tests among people with asthma and the benefits of limiting exposure to known allergens as a part of effective asthma management (see Chapter 6, Managing Allergy in the Asthma Patient). The patient may be referred to a specialist in the field of allergy who will evaluate the patient's exposure to allergens. In the absence of such referral, information about allergens may be obtained through a careful history and screening test for specific allergens, particularly for those patients with perennial symptoms and perennial allergen exposure (e.g., animal dander and house-dust mites).
- Rhinoscopy.
- Sinus x-rays.
- Bronchoprovocation with methacholine, histamine, or exercise challenge (see Chapter 2, Objective Measures of Lung Function, and Chapter 9, Exercise-Induced Asthma).
- Provocative challenge with occupational allergens (chemicals) (see Chapter 10, Special Considerations).
- Evaluation of pH for gastroesophageal reflux (see Chapter 10, Special Considerations).

There is no one test or set of tests that should be ordered for every patient. Individualized selection of diagnostic procedures is essential. However, with careful attention to the history, physical examination, and laboratory results, a correct diagnosis of asthma will be made in virtually all instances. In addition, this information will give the clinician a data base that will enable him or her to assess the degree of severity of asthma, to identify etiologic and aggravating factors, and to plan an appropriate course of therapy based on severity of illness.

General Guidelines for Referral to a Specialist

Referral to a specialist in asthma care (usually an allergist or pulmonologist) is appropriate under certain circumstances when:

- Patient has had a life-threatening acute asthma exacerbation, has poor self-management ability, or has difficult family dynamics.
- Signs and symptoms are atypical or there are problems in differential diagnosis (e.g., chronic bronchitis vs. asthma in adults, chronic cough in children, cystic fibrosis or bronchopulmonary dysplasia in a child who has a clinically important reactive airway disease component).
- Clinical entities complicate airway disease (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis).
- Additional diagnostic testing is indicated (e.g., skin testing, rhinoscopy, bronchoscopy, complete pulmonary function studies, provocative challenge).
- Patient is not responding optimally to the asthma therapy.
- Patient requires guidance on environmental control, consideration of immunotherapy, smoking cessation, complications of therapy, or difficult compliance issues.

Differential Diagnosis of Asthma

Underdiagnosis of asthma is a frequent problem, especially among young children, and occurs most often when young children who wheeze only when they have respiratory infections are dismissed as having wheezy bronchitis, asthmatic bronchitis, bronchitis, or pneumonia, despite evidence that the signs and symptoms are most compatible with a diagnosis of asthma.

Although recurrent episodes of cough and wheezing are almost always due to asthma in both children and adults, the clinician needs to be aware of other causes of airway obstruction leading to wheezing. There are long lists of differential diagnostic possibilities, but the more likely problems in infants, children, and adults are:

- Infants and children
  - —Obstruction involving large airways
    - Foreign body in trachea, bronchus, or esophagus.
    - Vascular rings.
    - Laryngotracheomalacia.
    - Enlarged lymph nodes or tumor.

- Laryngeal webs.
- Tracheostenosis or bronchostenosis.

—Obstructions involving both large and small airways
- Asthma.
- Viral bronchiolitis.
- Cystic fibrosis.
- Chlamydia trachomatous infection.
- Obliterative bronchiolitis.
- Bronchopulmonary dysplasia.
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux (see Chapter 10, Special Considerations).
- Vascular engorgement.
- Pulmonary edema.

■ Adults
—Mechanical obstruction of the airways.
—Laryngeal dysfunction.
—Chronic bronchitis.
—Pulmonary emphysema.
—Congestive heart failure.
—Pulmonary embolism.
—Pulmonary infiltration with eosinophilia.
—Cough secondary to drugs (beta blockers and/or angiotensin-converting enzymes (ACE) inhibitors).

Figure 1-4 presents an algorithm for diagnosing asthma that may be a useful guide in the differential diagnosis.

Classification of Asthma by Severity of Disease

Defining an individual's asthma as mild, moderate, or severe enables the clinician to categorize the overall assessment of a patient's asthma and select appropriate therapy. Figure 1-5 describes a classification of asthma based upon severity before optimal therapy is initiated. The characteristics are general, and because asthma is highly variable, these characteristics may overlap. Furthermore, an individual may switch into different categories over time.

The Role of Allergy in Asthma

An association between asthma and allergy has long been recognized. It has been reported that 75-85 percent of patients with asthma have positive immediate skin test reactions to common inhalant allergens.[1] Although these figures probably overestimate the number of patients with asthma in whom allergic factors are important, they do suggest that allergy must be considered in both the diagnosis and treatment of asthma.

The allergic reaction in the airways is significant for two reasons: (1) it can cause an immediate reaction, with bronchial obstruction, and (2) it can precipitate a late bronchial obstructive reaction several hours after the initial exposure. The delayed bronchial response is associated with an increase in airway hyperresponsiveness to nonimmunologic stimuli and can persist for several weeks or more after a single allergen exposure.[2] The basis for the late bronchial response and increased airway hyperresponsiveness is thought to be inflammation and, perhaps, secondary epithelial damage in the airways.

Importance of Allergy in Different Age Groups

Infants

In infants, viral respiratory infections are the principal trigger of asthma.[3] Allergens play a less important role in this age group than at other ages because it takes time for allergic sensitivity to develop. Although allergic reactions to food may occur in infants, foods are not common triggers of asthma. An elimination diet is not routinely recommended because it only rarely will reveal a previously unsuspected food as a cause of asthma in children.

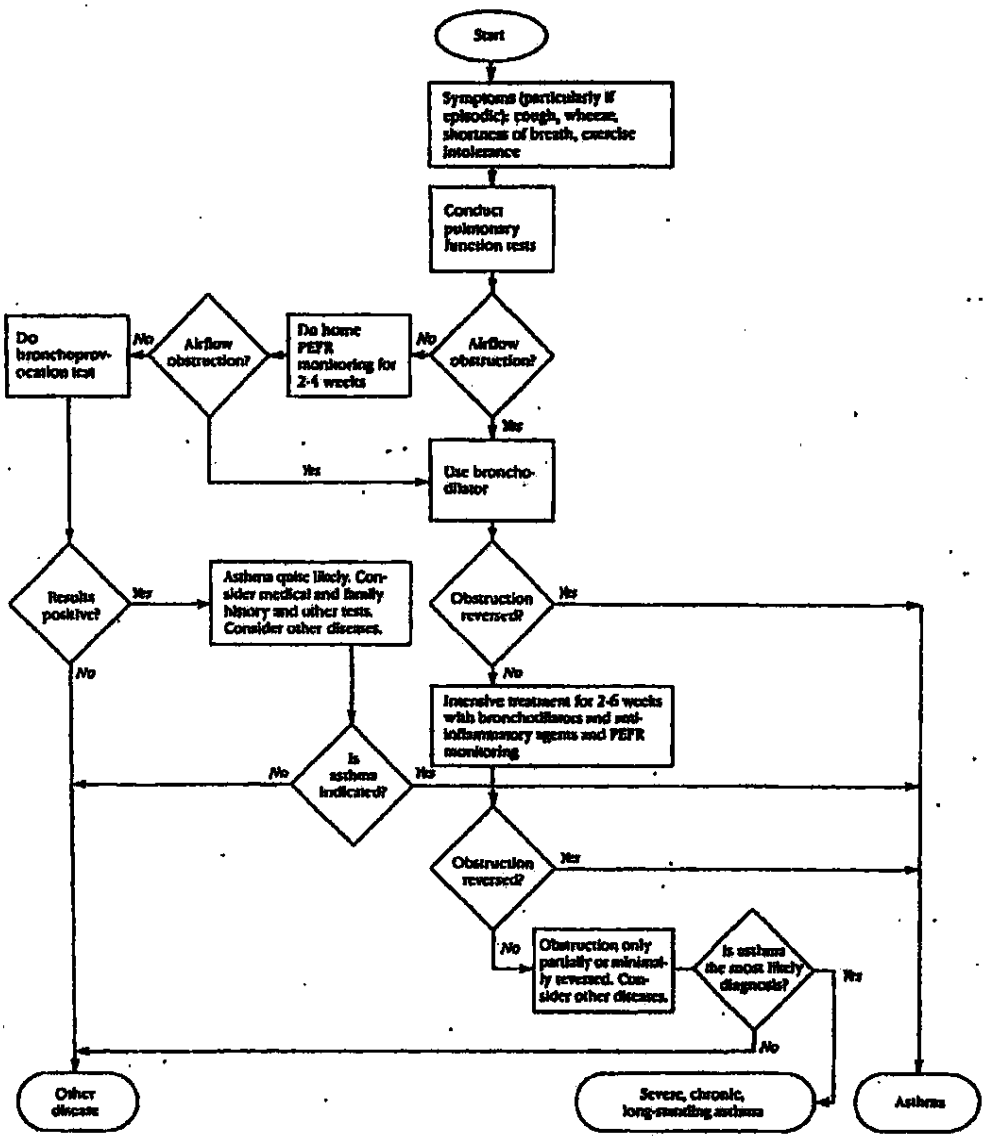
Children

Studies in children with asthma suggest that allergy influences the persistence and severity of the disease. Several authors have reported that the severity of childhood asthma correlates with the number of positive immediate skin tests.[4,5] Children with multiple positive skin tests are also more likely to have daily rather than intermittent asthma,[6] possibly because of the presence of a chronic allergic inflammatory process. The important allergens in children after infancy appear to be inhalants (see Chapter 6, Managing Allergy in the Asthma Patient).

Adults

Aeroallergens remain important in patients whose disease began prior to age 30 or who are exposed to occupational allergens (see Chapter 10, Special Considerations). Patients can also experience allergy for the first time over age 30. In adults, the intensity of allergen skin test reactivity does not appear to be associated with increased severity of asthma.[7] Food allergies do not commonly trigger asthma in adults. Patients may have a sensitivity to aspirin, a sensitivity which is not, however, on an immunologic basis (see Chapter 10, Special Considerations).

Figure 1-4
Algorithm for Diagnosing Asthma



Asthma is characterized by reversible airflow obstruction and can often be diagnosed with complete certainty. However, when mixed signals are present clinically, one must consider other diseases that can also cause airflow obstruction. Sometimes it may be impossible to distinguish among several possibilities or there may actually be coexisting diseases. This disclaimer is, in essence, true with any diagnosis.

The general approach for asthma is first to determine whether the patient has symptoms of cough, wheezing, shortness of breath, or exercise intolerance. Do they appear to be episodic in nature? If so, the diagnosis of asthma should be strongly considered, and efforts should be made to demonstrate with pulmonary function tests the reversibility of airflow obstruction after treatment. If airflow obstruction is present but does not immediately reverse with an inhaled bronchodilator, it may be necessary to treat the patient aggressively with bronchodilators and anti-inflammatory agents for up to 6 weeks before deciding that airflow obstruction is truly not reversible. If the symptoms present suggest asthma but there is no evidence of airflow obstruction, a bronchoprovocation should be performed. If the bronchial challenge is positive, then once again the diagnosis of asthma should be strongly considered.

At the point of strongly considering asthma, one should consider other diseases with reversible airflow obstruction, such as heart disease, the presence of foreign bodies in airways, and chronic obstructive pulmonary disease with a reversible component. If such diseases are present, and there are many to consider, one must try to determine whether this disease is predominant or whether asthma also coexists. When there is more than one disease present that can cause airflow obstruction, a conclusive diagnosis is difficult.

Modifying factors that increase the probability of asthma include such things as a personal or family history of asthma, hay fever, or other allergies. It should be remembered at this point, however, that there are two ages of onset of asthma. Asthma that begins in childhood almost always has a strong history of allergy and is likely to be atopic.

One final consideration: Some patients with severe, longstanding, and poorly treated asthma may develop irreversible airflow obstruction. These patients still may deserve a diagnosis of asthma if all other factors lead to that diagnosis, and if no other good cause for the airflow obstruction is found.

Figure 1-2

Clinical Classification of Asthma by Severity of Disease*

Characteristics	Mild	Moderate	Severe
A. Pulmonary			
Frequency of exacerbations	Exacerbations of cough and wheezing no more often than 1-2 times/week.	Exacerbation of cough and wheezing on a more frequent basis than 1-2 times/week. Could have history of severe exacerbations, but infrequent. Urgent care treatment in hospital emergency department or doctor's office <3 times/year.	Virtually daily wheezing. Exacerbations frequent, often severe. Tendency to have sudden severe exacerbations. Urgent visits to hospital emergency departments or physician's office >3 times/year. Hospitalization >2 times/year, perhaps with respiratory insufficiency or, rarely, respiratory failure and history of intubation. May have had cough syncope or hypoxic seizures.
Frequency of symptoms	Few clinical signs or symptoms of asthma between exacerbations.	Cough and low grade wheezing between acute exacerbations often present.	Continuous albeit low-grade cough and wheezing almost always present.
Degree of exercise tolerance	Good exercise tolerance but may not tolerate vigorous exercise, especially prolonged running.	Exercise tolerance diminished.	Very poor exercise tolerance with marked limitation of activity.
Frequency of nocturnal asthma	Symptoms of nocturnal asthma occur no more often than 1-2 times/month.	Symptoms of nocturnal asthma present 2-3 times/week.	Considerable, almost nightly sleep interruption due to asthma. Chest tight in early morning.
School or work attendance	Good school or work attendance.	School or work attendance may be affected.	Poor school or work attendance.
Pulmonary function			
• Peak Expiratory Flow Rate (PEFR)	PEFR >80% predicted. Variability** <20%.	PEFR 60-80% predicted. Variability 20-30%.	PEFR <60% predicted. Variability >30%.
• Spirometry	Minimal or no evidence of airway obstruction on spirometry. Normal expiratory flow volume curve; lung volumes not increased. Usually a >15% response to acute aerosol bronchodilator administration, even though baseline near normal.	Signs of airway obstruction on spirometry are evident. Flow volume curve shows reduced expiratory flow at low lung volumes. Lung volumes often increased. Usually a >15% response to acute aerosol bronchodilator administration.	Substantial degree of airway obstruction on spirometry. Flow volume curve shows marked concavity. Spirometry may not be normalized even with high dose steroids. May have substantial increase in lung volumes and marked unevenness of ventilation. Incomplete reversibility to acute aerosol bronchodilator administration.
• Methacholine sensitivity	Methacholine PC_{20} >20 mg/mL***	Methacholine PC_{20} between 2 and 20 mg/mL	Methacholine PC_{20} <2 mg/mL
B. After optimal treatment is established			
Response to and duration of therapy	Exacerbations respond to bronchodilators without the use of systemic corticosteroids in 12-24 hours. Regular drug therapy not usually required except for short periods of time.	Periodic use of bronchodilators required during exacerbations for 1 week or more. Systemic steroids also usually required for exacerbations. Continuous around-the-clock drug therapy required. Regular use of anti-inflammatory agents may be required for prolonged periods of time.	Requires continuous, multiple around-the-clock drug therapy including daily corticosteroids, either aerosol or systemic, often in high doses.

*Characteristics are general; because asthma is highly variable, these characteristics may overlap. Furthermore, an individual may switch into different categories over time.

**Variability means the difference either between a morning and evening measure or among morning peak flow measurements each day for a week.

***While the degree of methacholine/histamine sensitivity generally correlates with severity of symptoms and medication requirements, there are exceptions. See Chapter 2, Objective Measures of Lung Function, Section C, Bronchoprovocation.

Diagnosing Allergy in the Asthma Patient

The Medical History

Purpose. A thorough history is the primary method of determining whether or not a patient's asthma has a significant allergic component. Figure 1-6 provides a sample checklist for a patient questionnaire or interview.

The history is important in establishing a relationship between exposure to the allergen and the occurrence of symptoms. This relationship is most easily established with allergens that have a limited season and most difficult with allergens continuously present in the home, such as animal dander and mite allergens.

Special issues. Symptoms produced by allergens in the home will be aggravated if the patient is present during housecleaning activities. In addition, there may be some tendency for symptoms to worsen during the winter months.[4]

Useful information on the importance of pets in the home can often be gained by determining if symptoms improve when the patient is away from pets or the home for 1-2 weeks.

Great diversity exists in winter temperatures and levels of humidity in the United States. These factors have a profound effect not only on the species of wind-pollinating plants and their months of pollination but also on the prevalence of house-dust mites, cockroaches, and indoor and outdoor molds. In general, tree pollen may be present from February through May, grasses from May to June, weeds from August to October, and outdoor molds throughout the warm months.

Skin Testing or In Vitro Determinations of Specific IgE

If allergy is suspected and the patient's history is not sufficient to identify asthma triggers, consultation and appropriate skin testing by an allergy specialist (see Laboratory Studies) should be considered. Skin tests or in vitro tests, which can determine the presence of allergy to specific agents, should be considered for patients with asthma symptoms of at least moderate severity.

The results are used to define an appropriate environmental control program for the patient so that exposure to specific allergens can be reduced.

A positive skin test is necessary to diagnose allergy because clinical sensitivity to an aeroallergen is unusual in the absence of a positive skin test. Nevertheless, one may encounter many positive tests that do not have clinical relevance because the synthesis of IgE is not unique to clinically allergic individuals. Because of a high prevalence of clinically insignificant sensitivity, the patient's medical history is extremely important in confirming a diagnosis of clinically significant allergy.

Figure 1-6
Patient Interview Checklist for Assessing the Possible Role of Allergy in Asthma

- ☐ Is asthma worse in certain months? If so, are there symptoms at the same time of allergic rhinitis—sneezing, itching, nose runny and obstructed at the same time? (pollens and outdoor molds)*
- ☐ Do symptoms appear when visiting a house where there are indoor pets? (animal dander)
- ☐ If there are pets in the patient's home, do symptoms improve when the patient is away from home for a week or longer? Do nasal, eye, and chest symptoms improve? Do the symptoms become worse the first 24 hours after returning home? (animal dander)
- ☐ Do eyes itch and become red after handling the pet? If the pet licks the patient, does a red, itchy welt develop? (animal dander)
- ☐ Do symptoms appear in a room where carpets are being vacuumed? (animal dander or mites)
- ☐ Does making a bed cause symptoms? (mites)
- ☐ Do symptoms develop around hay or in a barn or stable? (molds and mites)
- ☐ Do symptoms develop when the patient goes into a damp basement or a vacation cottage that has been closed up for a period of time? (molds)
- ☐ Do symptoms develop related to certain job activities, either at work or after leaving work?
- ☐ If symptoms develop at work, do they improve when away from work for a few days?

**Possible causes of symptoms are enclosed in parentheses.*

In vitro laboratory tests may be used in place of skin tests. They yield the same information but usually with a lesser degree of sensitivity and at greater expense.

The performance of any allergy testing, be it in vivo (skin testing) or in vitro, should always be accomplished in the context of a history and physical examination taken by the physician who will be able to interpret the tests.

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2
Objective Measures of Lung Function

Pulmonary function studies are essential for diagnosing asthma and assessing the severity of asthma in order to make appropriate therapeutic recommendations. The use of objective measures of lung function is recommended because patient symptom reports and physical examination findings often do not correlate with the variability and severity of airflow obstruction. There are three sections to this chapter. The first section discusses spirometry in the medical setting for the initial assessment and periodic evaluation of patients with asthma. The second section discusses the use of peak expiratory flow rate measurement in medical settings and patients' homes for monitoring the course of asthma. The third section discusses bronchoprovocation for assessment of airway hyperresponsiveness.

Spirometry

Pulmonary function has traditionally been assessed by obtaining objective values that measure lung volumes or flow rates produced with maximum expiratory effort. Lung volumes can be measured by fairly sophisticated techniques, including plethysmography and gas dilution. However, the most practical technique of measuring volumes and flow rates is with the spirometer, which is limited to measuring only those volumes that can be expelled from the lung. Spirometers measure the vital capacity, the tidal volume, the expiratory reserve volume, and the inspiratory capacity of the lungs. One type of spirometer uses a bell displaced by air over water. Other types use a wedge or bellows and are electronic.

Abnormalities of lung function are categorized as restrictive and obstructive defects. Identifying the type of defect does not identify the specific anatomical or pathological defect, but specific disease processes are often associated with each type. Restrictive defects are diagnosed when the primary abnormality is reduction in lung volume with no apparent airflow obstruction. Restrictive defects are often associated with parenchymal lung disease or limitation of chest wall movement. Obstructive defects result from impairment of airflow through the trachea and bronchi leading from the alveolar sacs. Bronchial secretions, bronchospasm, loss of supporting structure, or edema of the bronchial wall lead to obstructive impairment.

Poor perception of asthma severity is a major reason for delays in treatment which may increase asthma severity and mortality. Conduct spirometry for initial and periodic patient assessment. Consider home PEFR monitoring for patients with moderate to severe asthma.

In analyzing lung function, the vital capacity is the most important volume in assessing patient effort and the presence of a restrictive component to the disease. To determine whether the reduction in vital capacity is due to restriction or obstruction, measurements of flow rate are obtained. Flow rates may be measured directly or determined by noting the volume expired over a period of time. Timed volumes measured on the spirometer include:

- *Peak expiratory flow rate (PEFR):* The maximum flow rate that can be generated during a forced expiratory maneuver; measured in liters per second, this measurement requires maximum effort for accuracy.
- *Forced vital capacity (FVC):* Total volume of air expired as rapidly as possible.
- *Forced expiratory volume 1 second (FEV_1):* The volume of air expired in 1 second from maximum inspiration.
- *Maximum midexpiratory flow rate (MMEF):* The slope of line between 25 percent and 75 percent of the forced expiratory volume.

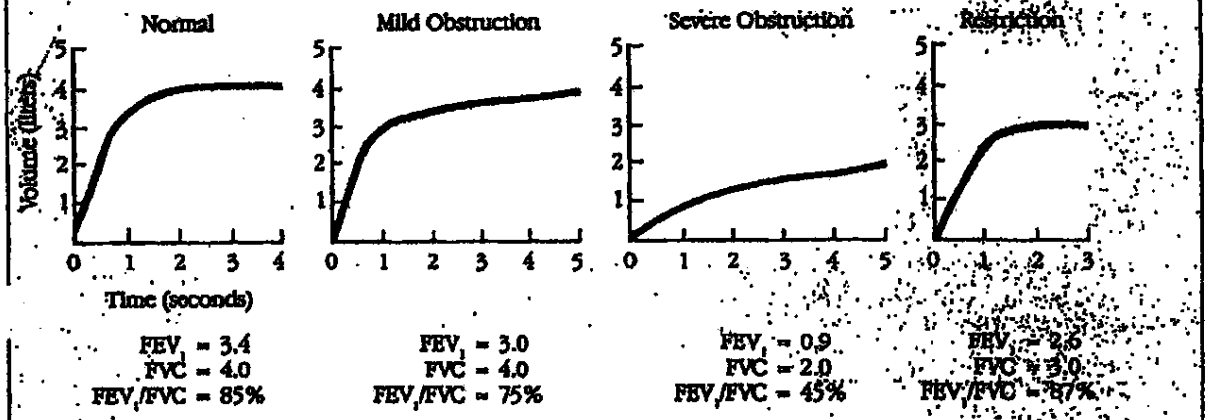
All patients suspected of having asthma should have office spirometry performed, at minimum, for initial assessment. Most physicians' offices can successfully use an office spirometer to make objective measurements of pulmonary function. It is important to use correct techniques and equipment that meet established standards.[1] When office spirometry is abnormal, a set of complete pulmonary functions done in a specialized pulmonary testing facility should be considered. For individual cases with complex questions, periodic assessment in a specialized pulmonary testing facility should be considered.

In many cases, clinical decisions can be made with the use of spirometry alone (see Figure 2-1).

- A reduced vital capacity and a normal flow rate are consistent with restrictive defect. Occasionally, the FEV_1 is reduced concomitantly with the reduction of the vital capacity. The flow rate can then be determined by assessing the percentage of the FEV_1 over the FVC: if there is no obstruction, this ratio is greater than 75 percent, and with severe restriction, the rate will approach 90 percent.
- A normal vital capacity with either impaired FEV_1 or impaired MMEF indicates pure obstruction. When the FEV_1 is severely reduced with clear evidence of obstruction (FEV_1/FVC ratio of less than 75 percent), the vital capacity can also be reduced due to severe obstruction alone.

Figure 2-1
Interpretation of Results of Spirometry*

Parameter	Restrictive	Obstructive
FVC	↓	Normal or ↓
FEV_1	Normal or ↓	↓
FEV_1/FVC	Normal or ↑	↓
FEF_{25-75}	Normal, ↓, ↑	↓



*The graph depicted is for illustration only. The interpretation of flow rates may vary with the age of the patient.

■ When the question of a mixed restrictive and obstructive defect occurs, further studies are necessary.

■ When the maximum midexpiratory flow rate is the only abnormal finding, mild airflow obstruction is present, indicating small airway disease.

The midexpiratory flow rate is useful as a screening maneuver but is too sensitive to assess the severity of obstruction. The FEV_1 is the single best measure of pulmonary function for assessing severity, although the peak expiratory flow rate, when done with good effort, correlates quite well with the FEV_1 and is in many cases much more convenient to obtain under a variety of circumstances.

When treating asthma patients, it is often necessary to make frequent objective assessments of flow rates, sometimes more than once a day. Day-night (circadian) variations in asthma and peak expiratory flow variability indicate the degree of bronchial hyperresponsiveness. These observations are a guide to the severity of airway inflammation.[2,3] The office spirometer may be too cumbersome and inconvenient for such frequent assessment. The peak expiratory flow rate measurement alone has been accepted as an independent measure of lung function. Its application has been useful in the home, clinic, and emergency department in the management of asthma.[4-10]

Many studies have demonstrated that symptom reports do not always reflect pulmonary function in asthma. For example, one study demonstrated that 22 people with asthma, ages 16 to 45, recovering from an acute asthma exacerbation reported freedom from symptoms at a point when the mean values of several objective parameters (i.e., airway resistance and conductance, FEV_1, maximum forced expiratory flow [$FEF_{\_\_}$], FEF_{25-75}) remained markedly abnormal.[8] Thus, patient status can be more accurately assessed with a simple measure of peak expiratory flow rate, particularly if attention is paid to training the patient to use maximum effort.

A review of various inexpensive compact instruments revealed that inter- and intrainstrument accuracy in measuring peak flow and correlation with FEV_1 was quite good.[12] Further work in evaluating the peak flow meter will be important, but the portable nature of the peak flow meter allows longitudinal monitoring in the hospital and at home.[13]

It is recommended that peak expiratory flow rate be used as the objective parameter to follow in assessing symptoms and making therapeutic recommendations when such recommendations depend on the severity of airflow obstruction. Peak expiratory flow rate measurements are useful in following both the course of asthma and a patient's response to therapy, but they are not sufficient to make a diagnosis or to fully evaluate the physiologic impairment associated with asthma. Therefore, it is recommended that office spirometry be conducted in the initial assessment of all patients with, or being evaluated for, asthma, and periodically thereafter as appropriate. It is recommended that clinicians consider using PEFR measured by peak flow meters at home to monitor patients over 5 years old with moderate to severe asthma.

Peak Expiratory Flow Rate Measurement

Peak expiratory flow rate (PEFR) is the greatest flow velocity that can be obtained during a forced expiration starting with fully inflated lungs (total lung capacity).[1] PEFR measurement has many benefits. It provides a simple, quantitative, reproducible measure of airway obstruction that can be obtained using inexpensive, portable peak flow meters. PEFR correlates well with forced expiratory volume at 1 second (FEV_1) measured by spirometry.[2] PEFR is an objective measurement that is analogous to measuring blood pressure with a sphygmomanometer.

The primary limitation of PEFR measurement is that it is effort dependent. Valid measurements depend on the patient's willingness and ability to exhale as hard as possible each time peak expiratory flow rate is measured. In addition, PEFR measures only large airway function; therefore, patients with mild asthma whose pathophysiologic abnormalities are linked to the small airways may be underdiagnosed if spirometry, which measures flow rates at low lung volumes (i.e., FEF_{25}, FEF_{25-75}), is not performed.

Objective measurement of airflow obstruction, such as PEFR, in patients with asthma is desirable because subjective measurements, such as dyspnea and wheezing, by physicians and patients may be inaccurate. One study demonstrated that only 44 percent of physicians could estimate PEFR within 20 percent of the actual measured PEFR of patients.[3] By the time wheezing can be detected with a stethoscope, the PEFR has already decreased by 25 percent or more.[4] Patients' symptom reports are also unreliable indicators of airway obstruction.[5,6] Poor perception of the severity of asthma on the part of the patient and physician has been cited as a major factor causing delay in treatment and thus may contribute to increased severity and mortality from asthma exacerbations.[7] Another advantage of PEFR measurement is that when patients have access to peak expiratory flow rate information, they may use their medications less frequently[8] and more appropriately.[9]

Figure 2-2 summarizes the applications of PEFR measurement in various settings.

PEFR Measurement in Medical Settings

Peak expiratory flow rate measurement is an important clinical tool in the office, emergency department, and inpatient hospital service. It is valuable in medical care settings to:[9,14]

- Assess the severity of asthma as a basis for making treatment decisions, such as admission to or release from the hospital or initiation of oral steroids.
- Monitor response to therapy during an acute exacerbation.
- Monitor response to chronic therapy and objective justification for therapy to patient.
- Diagnose exercise-induced asthma.
- Detect asymptomatic deterioration in lung function in the office and intervene before it becomes more serious.
- Monitor degree of airflow obstruction during a series of office visits to assess the overall success of therapy.

It is recommended that clinicians who treat asthma patients have a peak flow meter in the office and emergency department for use as an objective measurement. If available, spirometry with graphic record is ideal for monitoring lung function in the office setting.

PEFR Measurement at Home, Work, or School

Clinical experience has shown that teaching patients to take PEFR measurements at home improves the clinician's ability to provide effective treatment. The following uses of home PEFR monitoring have been reported:[9-12, 14-20]

- Daily monitoring to detect early stages of airway obstruction and initiate therapy before obstruction becomes more serious.
- Monitoring the course of treatment, using objective criteria to initiate or terminate steps in the treatment plan.
- Determining when emergency medical care is needed.
- Obtaining multiple daily measures of air flow to investigate specific allergens or workplace exposures that may exacerbate symptoms.

Figure 2-2
Possible Applications of Peak Expiratory Flow Rate Measurement

Clinician's Office (Chronic Asthma and Acute Episodes)	Clinician's Office/ Emergency Department (Acute Episode)	Hospital	Home	School	Workplace
1. Classify severity of patient's asthma.	1. Assess severity of episode on arrival.	1. Follow course of asthma episode and therapy.	1. Self-monitor asthma to increase or decrease therapy.	1. Guide decisions by school personnel when student has acute episodes of asthma at school.	1. Detect occupational exposures inducing or exacerbating asthma.
2. Follow trends in patients (i.e., seasonal episodes, increase or decrease medications, effect of new medication).	2. Measure response to therapy.	2. Predict hospital discharge.	2. Detect increases in circadian variation in PEFR that predict instability of asthma.	2. Identify exercise-induced asthma.	
3. Exercise testing to determine exercise-induced asthma.	3. Assess the need for hospitalization.		3. Detect decreases in PEFR that indicate early deterioration of asthma.	3. Increase sports participation by using PEFR to determine need to increase treatment.	
4. Utilize objective information to guide therapy over telephone.			4. Identify "triggers" of asthma (e.g., seasons, environmental exposures, viral infections, exercise).	4. Detect asthma that is not under control.	
			5. Report changes in PEFR to physician for guidance over the phone.		

- Measuring day-night (circadian) variations in peak expiratory flow rate to assess the degree of bronchial hyperreactivity or instability of asthma.
- Facilitating communication between patient and clinician by providing objective assessment of asthma severity.
- Providing feedback to help patients who have poor perception of the severity of their obstruction.
- Helping patients distinguish between airway obstruction (asthma) and other causes of breathlessness (e.g., hyperventilation).

Based on such findings, it is recommended that clinicians consider initiating home peak expiratory flow rate monitoring with patients who have moderate or severe asthma, particularly those whose asthma is unstable (e.g., those who are not optimally controlled and/or who experience diurnal variation). Careful supervision by the clinician is needed to ensure that the patient keeps peak expiratory flow rate records up to date and takes appropriate actions.

Supervising Home PEFR Monitoring

Several elements appear to be essential for the successful integration of home peak expiratory flow rate monitoring into the treatment plan. The following guidelines should be used:

Educate the patient and family about the purpose and technique of home monitoring. Education should include:

- —How and when to use the peak flow meter.
- —How to record peak expiratory flow rate measurements in a diary (see Chapter 5, Patient Education).
- —How to interpret the measurements.
- —How to respond to changes.
- —What information to communicate to the clinician (including emergency department clinicians).

■ Explain how the clinician uses the home PEFR data to choose and evaluate treatment. The clinician should review the data regularly by telephone or during office visits.

How To Measure PEFR

Equipment

In addition to the standard office peak flow meter, several portable peak flow meters are available. Specific instructions are contained in the literature accompanying each meter. Because different brands and models of peak flow meters often yield different values when used by the same person,* patients should use the same model in the home and the clinician's office. Alternatively, the patient may bring his or her meter to the office to compare readings. Technical standards for peak flow meters have recently been established by a National Heart, Lung, and Blood Institute task force. They are available from the institute.

Technique for Measurement

Most adults, as well as children as young as 5 years of age, usually can perform peak expiratory flow rate measurement. The effort required to produce the measurement is a short maximal blast of air similar to that required in the initial effort to blow up a balloon. Because peak expiratory flow rate measurement is effort dependent, patients may need to be coached, initially, to give their best effort. Nose clips are unnecessary. Instruct the patient to:

1. Place the indicator at the base of the numbered scale.
2. Stand up.
3. Take a deep breath.
4. Place the meter in the mouth and close lips around the mouthpiece.
5. Blow out as hard and fast as possible. (A prolonged expiration is necessary when performing spirometry, but not in PEFR.)
6. Write down the achieved measurement or value.
7. Repeat the process two more times.
8. Record the highest of the three numbers achieved. Sample recording charts are in Chapter 5, Patient Education (see Figure 5-1, Sample Diaries); manufacturers often enclose charts with peak flow meters.

Frequency of Measurement

Frequency depends on the severity of asthma and the patient's individual requirements, as judged by the clinician. Figure 2-3 gives guidelines on where, when, and how often to measure PEFR.

Recording the PEFR Measurement

PEFR can be recorded in a table format or a graph (see Figure 5-1) in Chapter 5, Patient Education.

Interpreting the PEFR Measurement

Predicted values of PEFR are determined by height and age, using ranges that vary among peak flow meters. (Figure 2-4 presents sample nomograms. Refer to nomograms accompanying each meter for the appropriate, specific ranges.) However, many patients' PEFR values are consistently higher or lower than the average values of people at the same height. It is, therefore, recommended that PEFR objectives for therapy be based upon each patient's "personal best" rather than using a percent of normal predicted value. In many asthma patients, the personal best can only be obtained after a period of aggressive anti-inflammatory and bronchodilator therapy and should be considered in that context.

There may be wide variation between the a.m. and p.m. measurements of PEFR, particularly at the start of therapy before good control is achieved. PEFR variations occur because of timing of medication, circadian variation, and poor control of asthma. The highest PEFR value or the personal best usually represents a p.m. measurement after a period of maximum therapy.

It is important to establish personal best values when the patient is under effective treatment to prevent airway obstruction. During a monitoring period of 2-3 weeks (or longer, if necessary), the patient records peak expiratory flow rate measurements at least twice a day. The personal best is the highest peak expiratory flow rate measurement achieved in the middle of a good day after using a bronchodilator. A course of oral steroids may be needed to establish personal best peak expiratory flow rate values. If the personal best is <80 percent predicted value, more aggressive therapy and continued daily monitoring are indicated.

Peak expiratory flow rate objectives (personal best values) should be reevaluated yearly to account for growth in children and progression of disease in adults.

Figure 2-3
Where, When, and How Often To Measure Peak Expiratory Flow Rate

Clinician's Office/Emergency Department

Chronic Asthma

1. Use peak flow meter or spirometry to measure PEFR in all patients >5 years of age at each office visit for therapeutic judgments.
2. Measure to confirm exercise-induced asthma (see Chapter IX).

Acute Exacerbations

1. Measure PEFR during all acute asthma exacerbations in patients >5 years of age.
2. Measure PEFR after beta$_2$-agonist inhalation to judge response.
3. Measure PEFR just prior to discharge from emergency department.

Hospital

1. Measure in all hospitalized patients >5 years of age bid to qid to follow course of asthma therapy and plan discharge.
2. Teach patients use of PEFR in hospital and encourage self-recording.

Home

1. Consider measuring in all patients >5 years of age with moderate or severe asthma to monitor course of asthma.
   a. Initially bid before and after bronchodilator until asthma is well controlled.
   b. Then daily at the same time of day.
   c. If daily cannot be complied with, measure twice a day two or three times a week.
2. Measure diagnostically before and after exposure.
3. Measure during acute exacerbations to monitor course of exacerbation and response to therapy.

Using PEFR Measurements To Manage Asthma

To help patients manage their asthma at home, a system of peak expiratory flow rate zones has been suggested.[2,14] The specific zones are established as a function of the individual's personal best or predicted value, whichever is highest. The emphasis is not on an isolated reading but rather on the variability patients experience from their personal best or from one reading to the next. It is recommended that home monitoring be done morning and evening (about 7 a.m. and 7 p.m.). If patients take an inhaled medication, peak expiratory flow rate should be measured both before and after treatment.

The zone system has been adapted to a traffic light system, to make it easier to use and remember.[2,15]

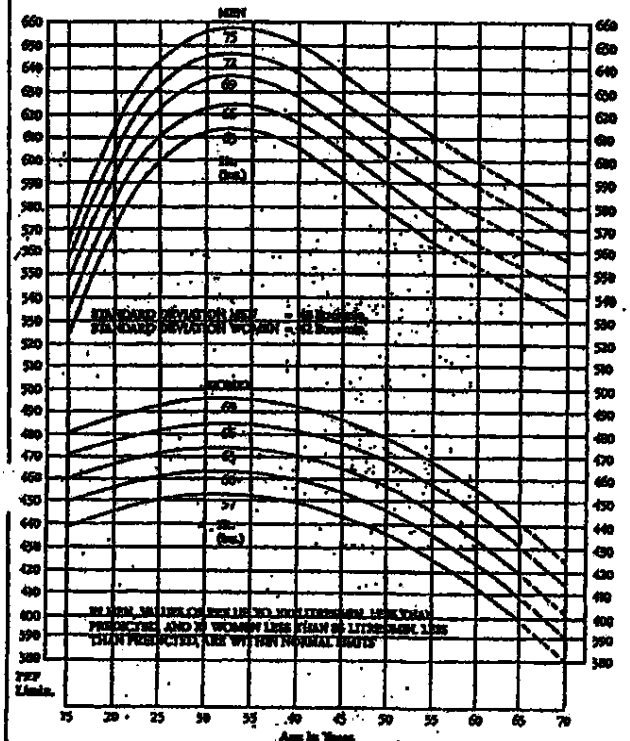
- Green (80-100 percent of personal best) signals all clear: No asthma symptoms are present and the routine treatment plan for maintaining control can be followed. For patients on chronic medications, consistent readings in the green zone may indicate an opportunity to consider a reduction in medications.
- Yellow (50-80 percent of personal best) signals caution: An acute exacerbation may be present and a temporary increase in medication may be indicated. Alternatively, the overall asthma may not be under sufficient control, and maintenance therapy may need to be increased.
- Red (below 50 percent of personal best) signals a medical alert: An immediate bronchodilator should be taken, and the clinician should be notified if PEFR measures do not return immediately and stay in yellow or green zones.

Some clinicians prefer zones with a smaller range (e.g., Green = 90-100 percent of personal best), especially for patients who experience rapid deterioration of their asthma.

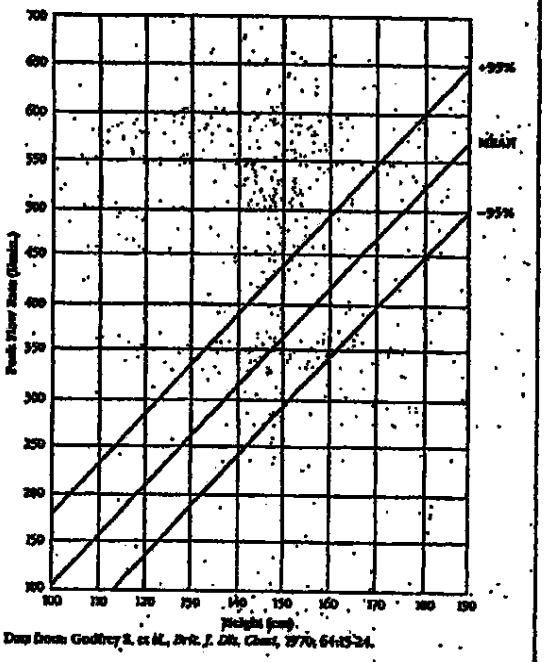
There are insufficient data to definitively establish zones for optimal therapy. The suggested zones are guidelines only; specific zones should be tailored by the clinician in recognition of individual patient circumstances.

Because the history and physical findings in asthma do not correlate with the variability and severity of air flow obstruction, it is recommended that the clinician consider having patients 5 years and older with moderate to severe asthma measure PEFR at home. In new patients, or to reassess continuing patients, this should be done twice a day before and

Figure 2-4
Sample Peak Expiratory Flow Rate Nomogram



Data from Nunn, AJ, Gregg, I, *Brit. Med. J.* 1989; 298:1068-70



Data from Godfrey S, et al., *Brit. J. Dis. Chest*, 1970; 64:15-24.

Table 1
Predicted Average Peak Expiratory Flow for Normal Males

(liters per minute)

Age	Height				
	60"	65"	70"	75"	80"
20	594	602	649	695	740
25	543	590	636	679	725
30	552	577	622	664	710
35	521	569	609	651	695
40	509	552	596	636	680
45	498	540	580	622	665
50	486	527	569	607	649
55	475	515	556	593	634
60	466	508	542	578	618
65	452	490	529	564	605
70	440	477	515	550	587

Data from Leiner GC, et al., Expiratory peak flow rate and Standard values for normal subjects. Use in a clinical test of ventilatory function. *Am Rev Resp Dis* 86:644, 1963.

Table 2
Predicted Average Peak Expiratory Flow for Normal Females

(liters per minute)

Age	Height				
	55"	60"	65"	70"	75"
20	390	425	460	496	529
25	385	418	454	490	525
30	380	415	448	485	516
35	375	408	442	476	509
40	370	402	436	470	502
45	365	397	430	464	495
50	360	391	424	457	488
55	355	386	418	451	482
60	350	380	412	445	475
65	345	375	406	439	468
70	340	369	400	432	461

Data from Leiner GC, et al., Expiratory peak flow rate. Standard values for normal subjects. Use in a clinical test of ventilatory function. *Am Rev Resp Dis* 86:644, 1963.

Table 3
Predicted Average Peak Expiratory Flow for Normal Children and Adolescents

(liters per minute)

Height (inches)	Males & Females	Height (inches)	Males & Females
43	147	56	329
44	160	57	344
45	175	58	347
46	187	59	350
47	203	60	378
48	214	61	387
49	227	62	406
50	240	63	413
51	254	64	427
52	267	65	442
53	280	66	454
54	295	67	467
55	307		

Data from Polgar, G, Promadhat, V *Pulmonary function testing in children: Normal values*. Philadelphia, W.B. Saunders, 1971.

Note: These tables are averages and are based on tests from a large number of people. An individual's PEFR may vary widely. Further, many individuals' PEFR values are consistently higher or lower than the average values. It is recommended that PEFR objectives for therapy be based upon each individual's "personal best," which is established after a period of PEFR monitoring while the individual is under effective treatment.

after treatment until asthma is well controlled and then either once daily in the morning or afternoon. If PEFR measurements are taken only once daily, they should be done at the same time and consistently either before or after bronchodilator. A few patients will not comply or their asthma will become extremely stable, and they may prefer to perform PEFR measurements intermittently. This method may lose the benefit of detecting early deterioration in lung function. However, if PEFR is being measured only two or three times a week, it is best to do both an a.m. and p.m. reading on the same day so that a >20 percent variation, which indicates worsening control of asthma, can be detected.

See Chapters 7 and 8 for further discussion of the use of peak expiratory flow rate measurements in determining medical care regimens.

Bronchoprovocation: Assessment of Airway Hyperresponsiveness

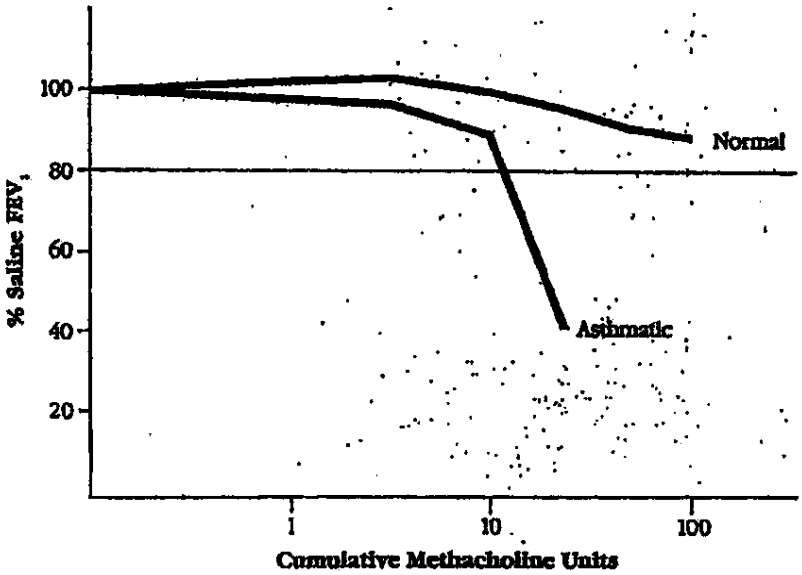
Airway hyperresponsiveness is the increased bronchoconstrictor response to a variety of physical, chemical, and pharmacologic stimuli.[3] Bronchodilator responsiveness is not always helpful in evaluating airway hyperresponsiveness because some people with asthma with normal pulmonary function and little reversibility after bronchodilator administration have elevated levels of airway responsiveness. Airway hyperresponsiveness can be better assessed in a specialized pulmonary testing facility using bronchial challenge or provocation techniques. The most commonly employed methods used to evaluate airway hyperresponsiveness include inhalation provocation with methacholine or histamine and exercise challenge (see Chapter 9, Exercise-Induced Asthma).

Changes in pulmonary function are measured with serial spirometry after inhaling incremental doses of an agonist such as methacholine or histamine or after exercise.[2] Results are expressed either as the cumulative dose or the concentration of agonist that produces a 20 percent fall in FEV_1. Results of exercise provocation are expressed as the peak fall in FEV_1 after exercise. People with asthma respond to bronchoprovocation with greater degrees of airflow obstruction than normal subjects[3] (see Figure 2-5). Some patients with allergic rhinitis, cystic fibrosis, and chronic obstructive lung disease, as well as normal subjects, especially after airway injury caused by viral infections or oxidant exposure, may also react to inhalation challenge but to a lesser degree than people with asthma.[4]

In asthma, the variation in a.m. and p.m. peak expiratory flow rate appears to reflect the presence of airway hyperresponsiveness. Monitoring of PEFR variation appears to be a convenient method to assess airway hyperresponsiveness clinically. Although people with asthma who have greater levels of airway hyperresponsiveness tend to have more severe asthma, there is individual variation, and some people with relatively mild asthma demonstrate high levels of airway responsiveness.[5] Thus, it seems premature to use results of a single bronchoprovocation test as the primary guide to therapy.

Nevertheless, bronchial challenge testing is helpful in the differential diagnosis of asthma when the respiratory history, physical findings, and PEFR variation are not adequate to confirm the clinical diagnosis of asthma. These situations include cough variant asthma and the evaluation of exercise-induced dyspnea.[1,6]

Figure 2-5
Asthmatic Response to Histamine or Methacholine Challenge



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3
Asthma Mortality

In 1988, 4,580 people died from asthma in the United States. The mortality rate for asthma has increased over the last decade (see Figure 3-1). Although the possibility of asthma-related death exists for all patients with asthma, several studies have revealed factors associated with an increased risk of asthma-related death. Practitioners who are treating asthma patients should be aware of these danger signs and take steps to minimize the risk of a fatal asthma exacerbation.

Risk Factors

Age

Asthma-related death rates among older age groups are higher than in any other age group and have increased substantially in the past 10 years (see Chapter 10, Special Considerations). Although the death rate is relatively low in young age groups, the trend of increasing asthma deaths in individuals from 5 to 34 years of age during this period of time has been noted.

People in their late teens and early twenties, particularly members of minority groups, are also overrepresented in asthma mortality statistics groups.

Ethnicity

African Americans have asthma-related mortality rates that are higher than those of Caucasians, especially in relatively young age groups, and the mortality rate in African Americans has increased significantly during the past decade. In 1979, African Americans of both sexes were about twice as likely to die of asthma as Caucasians. As Figure 3-1 shows, over the past decade this ratio has increased, and by 1987, the asthma death rate for all ages was almost three times higher among African Americans than Caucasians. However, in younger age groups (15-44 years of age), African Americans had death rates at least five times higher than their Caucasian counterparts.

Previous Life-Threatening Acute Asthma Exacerbations

Individuals who have had acute exacerbations of asthma that resulted in respiratory failure and required intubation are at increased risk for subsequent fatal exacerbations. Those who have experienced respiratory acidosis without requiring intubation are also considered high-risk patients.

The largest threat to the high-risk asthma patient is complacency about the severity of the disease—on the part of the patient, the physician, and the medical care system.

Hospital Admission for Asthma Within the Last Year

In 1987, there were more than 450,000 hospitalizations in which asthma was the first-listed diagnosis. Those hospitalized for asthma within the last year have a greatly increased risk of dying from asthma when compared with severity-matched asthma patients in the community who have not been hospitalized. Those with more than two hospitalizations for status asthmaticus in spite of long-term oral corticosteroid therapy are at the highest risk of dying from asthma.

Hospitalizations for asthma have been increasing among children. For example, from 1979 to 1987, the hospital discharge rate with asthma as the first-listed diagnosis rose 43 percent among children less than 15 years of age, from 19.8 to 28.4 discharges per 10,000 population. Among children, studies have found poverty to be associated with increased hospitalizations for asthma.[1]

Inadequate General Medical Management

Some people who die of asthma have progressive and poorly treated asthma, and the severity of the disease is not appreciated either by the physician or the patient. Because the severity of the disease is underestimated, underutilization of appropriate therapy is common among these patients.

In some patients, deterioration during an acute exacerbation occurs very rapidly. Underestimation of the severity of such exacerbations may lead to a life-threatening delay in starting medical treatment or seeking medical care.

Some patients may fail to appreciate a poor response to treatment during an acute exacerbation of asthma. Patients may rely on frequent repetitive use of inhaled beta$_2$-agonist far in excess of recommended doses for therapy at home (see Chapter 8, Management of Acute Exacerbations of Asthma). This treatment may temporarily blunt symptoms but mask increasing inflammation and airway hyperresponsiveness, which may, in turn, lead to abrupt and severe deterioration of lung function.

Without either the documented objective measures of pulmonary function or realization by the patient and/or the health care provider of the severity of the disease, risk of death is increased.

Psychological and Psychosocial Problems

Asthma, as other chronic diseases, may produce psychological reactions. Attention has been focused on the role of depression in asthma morbidity and mortality, particularly in children,[24]

which may lead to increased risk of death from asthma. Although the information linking depression and increased death from asthma is derived from clinical reports, the association is striking. In a review of cases in which children died suddenly and unexpectedly of asthma, there is clinical evidence that the children had expressed despair, hopelessness, a wish to die, and other evidence of depression.[4] Psychosocial problems that have been documented as associated with those at increased risk include alcohol abuse, documented depression, recent family loss and disruption, recent unemployment, and schizophrenia.[5]

Patients who have experienced a life-threatening asthma exacerbation have been observed, on the whole, to deny that they are at risk of death. Following a near fatal exacerbation of asthma, they tend to either develop decompensating psychiatric disease and symptoms of extreme anxiety or develop even higher levels of denial.[6] Some patients tend to minimize their symptoms and avoid access to health care.

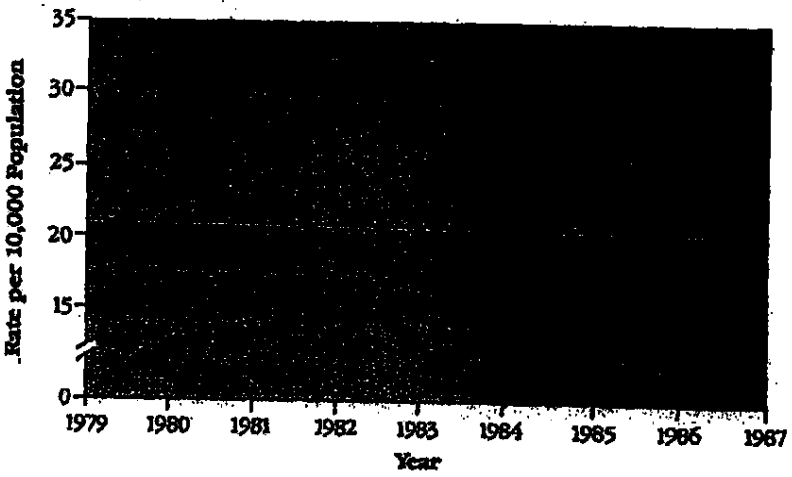
Regardless of the possible physiologic and psychologic interactions that link anxiety, depression, and asthma fatality, it is evident that patients who have these psychological disruptions are at increased risk for death and require specific professional intervention.

Lack of Access to Medical Care

Lack of access to medical care is another risk factor associated with asthma-related death. In rural areas, lack of access to adequate emergency care can result in life-threatening delays in medical treatment during asthma exacerbations. In some urban centers, more than half of the children with asthma may receive their entire asthma medical care in an emergency department.[7] Lack of access to either primary or specialist medical care, clinic routines, and reimbursement systems

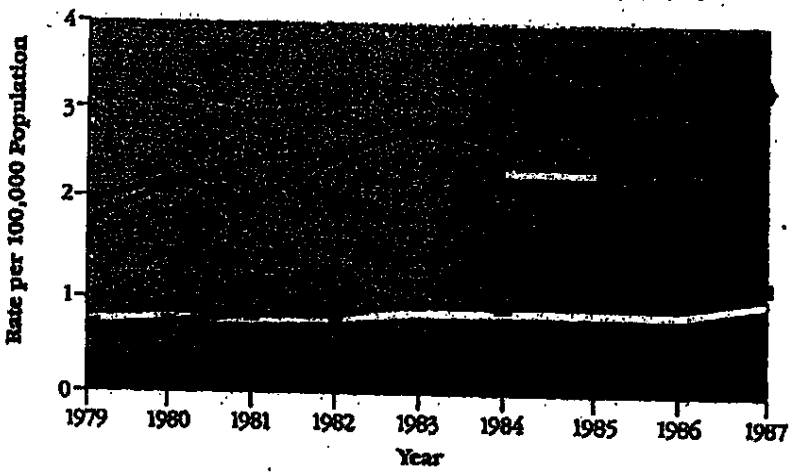
Figure 3-1
Trends in Mortality and Asthma Hospitalizations

Trends in Hospitalizations for Asthma



Source: National Hospital Discharge Survey, National Center for Health Statistics.

Trends in Asthma Mortality, U.S. Age-Adjusted Death Rates, 1979-1987



Source: Vital Statistics of the U.S., National Center for Health Statistics.

often makes it difficult and/or expensive for the underinsured or uninsured patient to enroll in the chronic, continuous asthma medical care programs necessary to manage the disease and prevent acute exacerbations.

Management of the Patient at Risk for Fatal Asthma

Suggestions for management of the patient at high risk for asthma-related death have not been "field tested" in controlled studies, but a number of approaches have been suggested.[3,4,9] The largest threat to the high-risk asthma patient is complacency—on the part of the patient, the physician, and the medical care system.

Recommended strategies include:

- Educating the patient and the family about asthma care. This is the foundation for managing asthma.
- Developing effective and simple drug regimens that patients can follow.
- Monitoring with special care those patients whose prednisone level is being reduced.
- Helping patients identify potential triggers in the work, school, or home environment.
- Monitoring the efficacy of environmental control measures and/or drug therapy with objective measures of lung function at regular intervals.
- Identifying which patients appear to be at increased risk for asthma-related death and identifying the specific factors that characterize the patient as high risk.
- Identifying high-risk patients and entering them into a special care followup program tailored to the individual patient's risk factors. Providing psychological support and utilizing mental health professionals and/or social services when appropriate.
- Preparing and periodically reviewing a crisis management plan for patient and family.
- Treating acute exacerbations promptly.
- Considering emergency calls from high-risk patients to be related to a severe exacerbation that may be fatal.[9]
- Monitoring the care of high-risk asthma patients in consultation with an asthma specialist.

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4
Overview of Approaches to Asthma Therapy

The effective management of asthma relies on both nonpharmacologic and pharmacologic therapies directed at reaching specific therapeutic goals. This chapter presents an overview of these approaches as a foundation for the specific asthma treatment recommendations delineated in the following chapters.

Goals of Therapy

Management of asthma should have the following goals:

- Maintain normal activity levels (including exercise).
- Maintain (near) "normal" pulmonary function rates.
- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion).
- Prevent recurrent exacerbations of asthma.
- Avoid adverse effects from asthma medications.

General Treatment Principles

Before reviewing specific therapeutic approaches to asthma, several general treatment principles should be considered.

- Asthma is a chronic condition with acute exacerbations. Treatment requires a continuous care approach to control symptoms, to prevent exacerbations, and to reduce chronic airway inflammation.
- Prevention of exacerbations is an important principle of therapy. This includes avoidance of triggers and, for allergic patients, the avoidance of allergens, especially in the indoor environment. It also includes around-the-clock medication treatment for many patients. Children and adults who have poor exercise tolerance, recurring symptoms, and frequent nocturnal symptoms—even patients with mild-moderate asthma—will often benefit from the regular administration and more aggressive use of antiasthma medication, especially anti-inflammatory medicine. In contrast, patients with mild intermittent asthma, uninterrupted sleep at night, and good exercise tolerance may require only occasional treatment for the relief of symptoms. Periodic assessment of these patients will assure that their therapy is appropriate.

Asthma therapy has four components: patient education, environmental control, comprehensive pharmacologic therapy and objective monitoring measures.

Whatever medication is used, a poor or short-lasting response to treatment mandates immediate medical care.

- The treatment of asthma should be based on an understanding of the underlying pathophysiologic mechanisms and on the objective assessment of the severity of the disease. The increased appreciation of the importance of inflammation in the pathogenesis of asthma has led to special interest in the use of medication with anti-inflammatory activity and has intensified the search for new therapeutic agents that can specifically counteract the effects of inflammatory mediators in the airways.[43] Thus, therapy should include efforts to reduce underlying inflammatory components in asthma and to relieve or prevent symptomatic airway narrowing. It is hoped that therapy will lead to reduction in airway hyperresponsiveness and prevention of irreversible obstruction.[47]
- Anticipatory or early interventions in treating acute exacerbations of asthma reduce the likelihood of developing severe airway narrowing.
- Asthma therapy has several integral components: patient education, environmental control, and pharmacologic therapy, as well as the use of objective measures to monitor the severity of disease and the course of therapy. Figure 4-1 illustrates the interrelationship of these approaches in the management and pathogenesis of asthma.

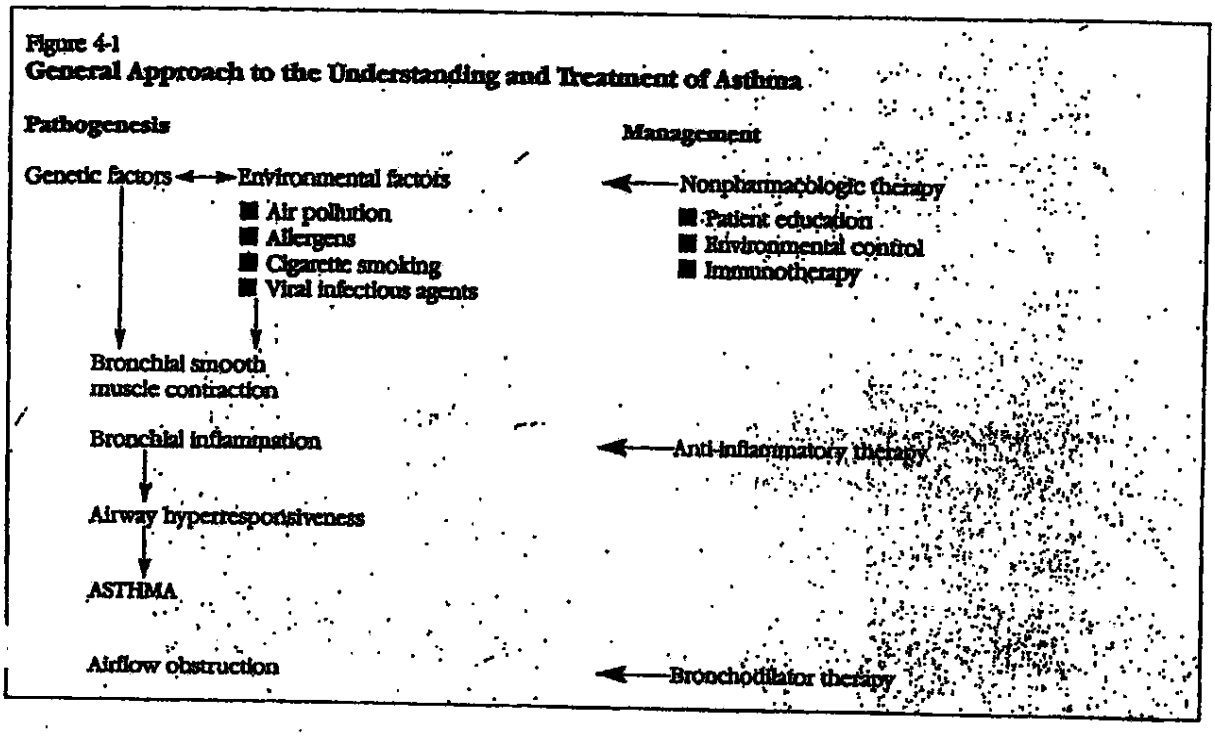
Nonpharmacologic Therapy

Optimal nonpharmacologic treatment of asthma includes consideration of the following:

- Patient and family education (see Chapter 5).
- Avoidance of agents that induce or trigger asthma (see Chapter 6, Managing Allergy in the Asthma Patient).
  - —Allergens.
  - —Irritants such as cigarette smoke.
  - —Reasonable attempts at reducing exposure to respiratory viruses.
- Appropriateness of immunotherapy (see Chapter 6).

Asthma patients, by definition, have hyperresponsive airways; therefore, avoidance of exposure to irritants that produce airway narrowing is essential. Irritants and allergens that provoke acute symptoms also increase airway hyperresponsiveness, and this, in turn, increases vulnerability to further irritant or allergen exposure.[4] Nonspecific irritants include tobacco smoke, dusts, strong odors, and industrial or environmental air pollutants. If allergy plays a role in an individual patient's disease, environmental control measures to avoid specific allergens are of paramount importance, and immunotherapy may be indicated in selected patients (see Chapter 6). The value of patient education as part of an optimal therapeutic program is well documented and is discussed in Chapter 5, Patient Education.

Figure 4-1
General Approach to the Understanding and Treatment of Asthma



Pharmacologic Therapy

Pharmacologic therapy is used to treat reversible airflow obstruction and airway hyperresponsiveness. Medications include bronchodilators and anti-inflammatory agents; some drugs may act as both. Anti-inflammatory agents interrupt the development of bronchial inflammation and have a prophylactic or preventive action. They may also modulate or terminate ongoing inflammatory reactions in the airways. Bronchodilators act principally to dilate the airways by relaxing bronchial smooth muscle.

- Anti-inflammatory agents include:
  - —Corticosteroids.
  - —Cromolyn sodium or cromolyn-like compounds.
  - —Other anti-inflammatory compounds.
- Bronchodilators include:
  - —Beta-adrenergic agonists.
  - —Methylxanthines.
  - —Anticholinergics.

The discussion below reviews pharmacologic approaches to asthma therapy that relate the choice of medication to the pathophysiology of asthma and therapeutic goals. Whatever medication is used, it is essential for both the patient and the clinician to recognize that a poor or short-lasting response to treatment in the face of progressively worsening asthma mandates immediate, intensive medical care. Indications of diminished control of asthma may be an increased use of bronchodilators or a lack of an expected therapeutic response to the administration of the medication. In fact, recent data suggest that increased patient use of bronchodilators on an outpatient basis in the face of worsening asthma may be associated with increased asthma morbidity and mortality.[9] A decreasing therapeutic response may develop over a short period of time, or gradually during a period of days to weeks. Failure to appreciate the severity of asthma or an inadequate response to therapy are major risk factors for morbidity and mortality during acute exacerbations of asthma.

Anti-Inflammatory Agents

Corticosteroids

Corticosteroids are the most effective anti-inflammatory drugs for the treatment of reversible airflow obstruction. While many mechanisms of action have been proposed, the most important are:

- Interference with arachidonic acid metabolism and the synthesis of leukotrienes and prostaglandins.

■ Prevention of the directed migration and activation of inflammatory cells.

■ Increased responsiveness of beta-receptors of the airway smooth muscle.

Corticosteroids may be administered parenterally, orally, or as aerosols.[11,12] During the past decade, there has been less fear of using short courses of oral (or parenteral) corticosteroids to treat severe acute exacerbations of asthma because the introduction of inhaled corticosteroids reduces the need for prolonged oral corticosteroids and facilitates withdrawal of short-course oral corticosteroids. It is clear that the duration and severity of an acute asthma exacerbation can be substantially reduced by therapy with corticosteroids.[12]

Early treatment of severe acute exacerbations of asthma with oral corticosteroids prevents progression of the asthma exacerbation, decreases the need for emergency department visits or hospitalizations, and reduces the morbidity of the illness. When oral corticosteroids are used to treat acute severe asthma, the onset of action is gradual, occurring approximately 3 hours after administration with peak effectiveness occurring about 6-12 hours after administration.[12]

Acute short-term corticosteroid therapy is begun with relatively high drug dosages (40-80 mg prednisone daily in adults or 1-2 mg/kg in children) and can be maintained up to 5-10 days or tapered over the same interval. Therapy with oral steroids should be maintained until peak expiratory flow rates are stable near personal best or predicted values.

The major adverse effects associated with high-dose short-term systemic therapy include reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face, mood alteration, hypertension, peptic ulcer, and aseptic necrosis of the femur.

In any patient requiring chronic therapy with oral corticosteroids, a trial of inhaled corticosteroids (which have minimal systemic effects) should be attempted to determine whether oral corticosteroid treatment can be reduced or eliminated. Oral steroids should be continued only if shown to reduce chronic symptoms substantially or reduce the frequency of severe episodes. Oral steroids should not be used alone without maximizing other forms of therapy. Long-term oral corticosteroid therapy in severe asthma is limited by the risk of significant adverse effects such as osteoporosis, hypertension, Cushing's syndrome, cataracts, myopathy, hypothalamic-pituitary-adrenal axis suppression, and, in rare instances, impaired immune mechanisms. Therefore, prolonged daily use of oral corticosteroids is reserved for patients with severe asthma (see Chapter 1, Definition and Diagnosis) despite use of high-dose inhaled corticosteroids. The lowest possible drug dose should be employed; alternate-day therapy should be attempted; the dose should be a single early-morning dose every 48 hours; and pulmonary function tests should be used to objectively assess efficacy.

Inhaled corticosteroids are safe and effective for the treatment of asthma.[4,13] There are infrequent systemic adverse effects associated with the use of inhaled steroids at doses currently approved in the United States.[14] Long-term high-dose regimens of inhaled corticosteroids are being utilized, and long-term followup studies are underway.[15] It has been demonstrated that the use of high doses of inhaled corticosteroids reduces the need for the chronic use of oral steroids, which have known adverse effects. Local adverse effects from inhaled corticosteroids include oropharyngeal candidiasis, dysphonia, and occasional coughing resulting from upper airway irritation caused by inhaling the corticosteroid aerosol.[14] These adverse effects can be reduced or prevented by administering corticosteroids with a chamber or spacer that reduces large particle deposition in the mouth and by rinsing the mouth with water after each use. Depending on the preparation, these agents are administered 2-4 times a day (see Chapters 7, Management of Asthma, and 8, Management of Acute Exacerbations of Asthma).

Because of the importance of airway inflammation in the pathogenesis of asthma, inhaled corticosteroids are being used more frequently as primary therapy for moderate and severe asthma. This approach not only provides symptomatic benefit but also reduces airway hyperresponsiveness.[4,13]

Cromolyn Sodium

Cromolyn sodium is currently the best nonsteroidal anti-inflammatory drug for asthma; similar drugs are under development and testing.[16] The exact mechanisms of action of cromolyn sodium are not fully understood, although the original theory that cromolyn sodium stabilizes and prevents mediator release from mast cells is still accepted.[16] Administered prophylactically, cromolyn sodium inhibits early- and late-phase allergen-induced airway narrowing and acute airway narrowing after exposure to exercise (but less so than inhaled adrenergic agents), cold dry air, and sulfur dioxide. There is no way to reliably predict whether a patient will respond to cromolyn sodium; a 4-6 week trial of cromolyn sodium therapy may be required to determine efficacy in individual patients.[16,17] Cromolyn sodium produces only minimal side effects, such as occasional coughing upon inhalation of the powder formulation. Thus, cromolyn sodium is an important therapeutic approach to the treatment of airway inflammation in asthma.

Anti-inflammatory Drugs Under Investigation

The following drugs are not currently approved for the treatment of asthma in the United States but are being tested in clinical trials:

■ *Nedocromil sodium.* This drug is a pyranoquinoline derivative and a prophylactic agent that inhibits mediator release in a variety of in vitro systems.[20] The drug also inhibits allergen-induced acute and late-phase asthmatic reactions and modulates allergen-induced increases in bronchial hyperresponsiveness. It also reduces the acute airway narrowing response to exercise, hyperventilation, mist, and sulfur dioxide. Clinical trials show that long-term therapy reduces nonspecific airway reactivity in atopic and nonatopic asthma patients.[5] Therapy with nedocromil is not associated with any significant adverse effects.[20] Further experience is required to determine its exact therapeutic profile.

■ *Antihistamines.* With the development of the new classes of nonsedating antihistamines, there has been renewed interest in their use.[21,22] These agents block the acute bronchoconstrictor effects produced by inhaled histamine. Some studies show that antihistamines have mild bronchodilator activity. The newer antihistamines also may inhibit mediator release from in vitro cell systems. Oral antihistamines have been shown to be superior to placebo in reducing symptoms in some asthma patients who are sensitive to grass and pollen. Thus, there is ongoing reevaluation of this class of compounds in asthma therapy. The long-held concern that antihistamines might worsen asthma as a result of a putative drying effect on bronchial mucus has not been verified.

■ *Ketotifen.* This oral prophylactic drug has antihistaminic activity. Ketotifen seems to be most effective in mild asthma and appears to require at least 4-12 weeks to show any significant clinical effect.[24] Other than sedation, few adverse effects have been reported. Although this drug is available in Europe and Japan, clinical trials performed in the United States have shown limited efficacy.

Approaches To Reduce Oral Corticosteroid Dependence

Treatment of patients with severe, persistent asthma who require high doses of systemic steroids presents a therapeutic challenge. Several innovative therapeutic regimens have been proposed to help reduce oral steroid dependence in severe asthma. Some of these approaches are experimental and should be used only in selected patients under the supervision of an asthma specialist.

High-dose Inhaled Corticosteroids

Before attempting any of the experimental therapies that are described below, a trial of high doses of inhaled corticosteroids (two to four times the usual daily dose) is recommended.[11,25] This approach is associated with the lowest incidence of adverse effects and has a high likelihood of clinical efficacy. In the steroid-dependent person with severe asthma, treatment with high-dose inhaled corticosteroids should be maintained over a period of several weeks to months, and the dose of oral steroids should be reduced slowly while monitoring pulmonary function (PEFR or FEV). This approach often results in better symptom control and a reduction in the dosage of oral steroids.

Experimental Steroid-sparing Drugs

■ *Troleandromycin (TAO).* Troleandromycin (TAO), a macrolide antibiotic, decreases the elimination rate of both theophylline and methylprednisolone.[26] It has been reported that the addition of TAO permits the dose of methylprednisolone to be decreased over the course of days to weeks, occasionally permitting the use of an alternate-day oral regimen in steroid-dependent patients with severe asthma. This drug effect is relatively specific for methylprednisolone. There may be steroid-enhancing effects because patients may become more cushingoid early in the course of TAO therapy. Some of the adverse steroid effects gradually disappear as the methylprednisolone dose is decreased. A chemical hepatitis may occur, but it is usually reversible when TAO is discontinued. The TAO-methylprednisolone regimen should be used only in steroid-dependent patients with severe asthma under the supervision of a physician who has experience in the use of this drug.

■ *Methotrexate.* Recently, methotrexate has been used in the treatment of steroid-dependent severe asthma because of its potent anti-inflammatory effect. The use of methotrexate has been reported to result in a reduction of oral corticosteroid dosage and better asthma control in some patients.[27] Common side effects of methotrexate therapy include nausea, vomiting, and abdominal pain. Less frequent but potentially more severe adverse effects involve hematologic and hepatic systems, as well as teratogenic and pulmonary effects. Methotrexate should be used only in patients with very severe asthma under the supervision of a physician who has experience in the use of this drug.

■ *Gold.* It has been reported that long-term therapy with oral gold may help to reduce corticosteroid requirements and may improve symptoms in severe steroid-dependent asthma.[28] In some patients there may be an associated reduction in nonspecific bronchial hyperresponsiveness. Controlled clinical trials are necessary to determine the precise role of oral gold therapy in the treatment of severe asthma.

Bronchodilators

Beta-adrenergic Agonists

The desirable pharmacologic effects of beta-adrenergic agonists (beta$_2$-agonists) in asthma therapy result from their action on beta$_2$-adrenergic receptors; their effects on beta$_1$ receptors may produce undesirable cardiovascular effects. Beta$_2$-agonists relax airway smooth muscle and may modulate mediator release from mast cells and basophils.[25, 26] Currently available beta$_2$-agonists have limited duration of action (4-6 hours). Longer-acting inhaled beta$_2$-agonists with action lasting 12-18 hours are under development. The newer adrenergic agonists are more selective for the beta$_2$ receptor and have a more prolonged duration of action, although they still retain some beta$_1$ cardiac activity.[26, 27]

Aerosol or inhaled therapy is comparable to or better than oral therapy in producing bronchodilation and causes fewer systemic adverse effects such as cardiovascular stimulation, anxiety, and skeletal muscle tremor. Inhaled therapy has a more rapid onset of action (especially when compared to the oral formulation) and a similar duration of action, even when administered in substantially lower dosages.[28] Furthermore, inhaled therapy is superior to oral therapy because oral beta$_2$-agonists cause more adverse effects and require higher doses to achieve similar effects. Because asthma is an airway disease, inhaled therapy with the beta$_2$-agonist delivered directly to the airways is usually preferable to systemic therapy. Inhaled beta$_2$-agonists are available in metered-dose inhalers as well as dry-powder capsules.

Beta$_2$-agonists are the medication of choice for treatment of acute exacerbations of asthma[29] and for the prevention of exercise-induced asthma. They can be used either intermittently to control episodic airway narrowing or chronically to aid in the control of persistent airway narrowing. Although beta$_2$-agonists are commonly used chronically, a recent study has questioned whether regular therapy with a specific beta$_2$-agonist may be associated with deterioration of control of asthma in some patients.[9]

Although adrenergic aerosols (inhaled beta$_2$-agonists) are currently among the safest drugs available for asthma therapy, there are some areas of concern.[27] Most deaths from asthma appear to be related to the severity of acute, irreversible airflow obstruction. However, adverse drug reactions specifically involving the cardiovascular system may also occur. Cardiovascular complications may result from decreased serum levels of potassium or direct stimulation of the myocardium.[30, 31] Adverse cardiovascular reactions may occur with the combination of systemic adrenergic agonists and theophylline.[27] However, cardiac arrhythmias and myocardial ischemia resulting from beta$_2$-agonist therapy usually occur in patients with preexisting cardiovascular disease, especially among the elderly.[32, 27]

Very rarely, patients with asthma may experience paradoxical bronchoconstriction as a result of inhaled beta$_2$-agonists administered by metered-dose inhalers (MDI).[33] A paradoxical response is an abrupt worsening of asthma symptoms and/or a decrease in expiratory flow rates shortly after inhaling a therapeutic aerosol. It is not clear how often the paradoxical response is caused by the therapeutic agent itself; in many cases, it appears to be due to another component or contaminant of the particular canister (MDI) or batch of canisters.[34]

A recent report associates the regular use (as opposed to prn, or as needed, use) of a potent inhaled beta$_2$-agonist with diminished control of asthma.[9] This study is in contradistinction to the conclusions of previous clinical trials that demonstrated an improvement in asthma symptoms with regularly scheduled treatment with inhaled beta$_2$-agonist.[35-42] The mechanism of diminished control is unclear; possibilities include the development of rebound airway hyperresponsiveness, increased bronchial secretions, or both. The recent report noted above suggests the need for reevaluation of the effects of regular therapy with inhaled beta$_2$-agonists on airway hyperresponsiveness in asthma. Several prospective studies have shown that chronic therapy with beta$_2$-agonists does not alter airway hyperresponsiveness.[43-46] However, some studies have reported slight increases in airway hyperresponsiveness during therapy[47-50] or rebound increases in airway hyperresponsiveness following cessation of the inhaled beta$_2$-agonist.[51] For the most part, these changes in airway hyperresponsiveness are small and may not be clinically significant.

Another potential reason for increased asthma symptoms during prolonged therapy with inhaled beta$_2$-agonists may be the development of tolerance or subsensitivity resulting from down-regulation of beta-adrenergic receptors.[44, 52] Most studies suggest that significant tolerance does not usually develop in patients with asthma.[53] When tolerance does occur, it is characterized by a small reduction in the bronchodilator response and by a slight shortening in the duration of action after inhaling a beta$_2$-agonist. Thus, tolerance is not usually of major clinical significance and does not diminish the overall usefulness of inhaled beta$_2$-agonists in asthma therapy. It is possible, however, that receptor downregulation could account for some of the diminished control of asthma and increased airway hyperresponsiveness reported during chronic regular beta$_2$-agonist therapy. Additional placebo-controlled studies are needed on the effects of regular versus intermittent therapy with inhaled beta$_2$-agonists on asthma

symptoms, airway hyperresponsiveness, and asthma mortality.

Methylxanthines

Theophylline, the principal methylxanthine used in asthma therapy, is a bronchodilator that may also have extrapulmonary effects.[28,29] For example, theophylline may augment respiratory muscle contractility, thus reducing respiratory muscle fatigue.[29] Theophylline may also possess at least some degree of anti-inflammatory activity although this is a subject of debate.[16,17] The precise mechanism of action of theophylline is not clear.[14] In vitro, theophylline inhibits phosphodiesterase, an enzyme that catalyzes the breakdown of cyclic AMP. However, the low concentrations of theophylline that are achieved in vivo are unlikely to have this pharmacologic action.

Because theophylline is eliminated from the body rapidly by some individuals, especially children, sustained-release products are used for chronic therapy.[14,30] During the past 10 years, a number of products have been introduced that offer the putative advantage of once-a-day dosing. Although once-a-day dosing may be satisfactory in those adults who eliminate the drug slowly, substantial peak-to-trough differences in theophylline serum concentration are found in individuals who eliminate the drug quickly. Furthermore, intestinal transit time in some patients is so rapid that sustained-release preparations which are designed to release drugs especially slowly (i.e., they have long absorption half-lives) will pass out of the gut before absorption is complete. The longer acting preparations may also be affected by the presence of food in the gut or by the fat content.[31] In some cases, the rate of drug release is greatly accelerated, and in other cases drug absorption is impaired. Other sustained-release products are relatively unaffected by food administration. Therefore, the physician should be familiar with the pharmacologic properties of the product selected.

Approximately 90 percent of orally administered theophylline is metabolized in the liver.[14] The drug's elimination rate is reduced by such factors as liver disease, congestive heart failure, and certain drugs that decrease its rate of elimination and may allow toxic concentrations to develop; these drugs include cimetidine, quinoline, antibiotics, troleandromycin (TAO), and, to a lesser extent, erythromycin. Theophylline clearance may also decrease during febrile illnesses. Individual differences in metabolism may require measurement of theophylline blood levels, especially when higher therapeutic levels are desired or when conditions known to alter theophylline metabolism exist. The dose of theophylline should be reduced in patients with cardiac and hepatic disease and when it is used in combination with drugs that lower its metabolic rate. In obese individuals (with greater than 120 percent ideal body weight), initial theophylline should be calculated on the basis of ideal rather than actual body weight to avoid overdosage.

Monitoring theophylline serum concentrations is an important part of acute care and long-term management of patients with asthma. The frequency with which theophylline monitoring should be performed is related to specific clinical situations. Monitoring is required for patients who fail to exhibit the expected bronchodilator effect while receiving an appropriate therapeutic regimen, as well as for patients who develop an adverse effect on the usual dose. It is useful to monitor serum theophylline concentration when an asthma patient begins theophylline therapy and then at some regular intervals, approximately 6-12 months thereafter, as long as no adverse effects are observed.

Although it has been shown that a steady-state serum concentration for the theophylline of between 10-20 μg/mL gives optimal effect, a more conservative approach would be to aim for levels between 5 and 15 μg/mL.[14,29] There appears to be a linear relation between log serum concentration and bronchodilator effect within this 5-15 μg/mL therapeutic range. Therefore, a patient's theophylline dose should be increased if symptoms persist and the patient is at the lower end of the serum concentration range. Serum concentrations under 15 μg/mL are generally not associated with theophylline toxicity.[32,33] The signs and symptoms of theophylline intoxication involve many different organ systems. Gastrointestinal symptoms—nausea and vomiting—are the most common early events. However, theophylline intoxication in adults can result in seizures, which may not be preceded by evidence of central nervous system stimulation. Cardiopulmonary effects include tachycardia, arrhythmias, and, occasionally, stimulation of the respiratory center (tachypnea). Diuresis, relaxation of the detrusor muscle (causing difficulty in urination in older men with prostatism), and important metabolic effects such as hyperglycemia and hypokalemia may also occur. The effects of theophylline on behavior and learning in children have received attention recently.[34,35] Because theophylline causes central nervous system stimulation, it may produce behavioral disturbances in children. Of more serious consequence are the reports that the use of theophylline is associated with impairment of learning. A review of these reports conducted by the Food and Drug Administration concluded that current data do not support the hypothesis of an adverse effect of theophylline on the performance of school children.[36]

Overall, theophylline has mild to moderate serum-concentration-dependent bronchodilator activity.[31,36] Because of its long duration of action when given as a sustained-release

product, it is particularly useful in the control of nocturnal asthma.[47] When used in combination with usual doses of inhaled beta-agonists, theophylline may produce additional bronchodilation.[48,49] Theophylline has the potential for significant adverse effects; however, these can generally be avoided by appropriate dosing and monitoring.

Anticholinergics

Anticholinergic therapy is the oldest form of bronchodilator therapy for asthma. Inhaled anticholinergic agents block postganglionic efferent vagal pathways.[50] When inhaled, these agents produce bronchodilation by reducing intrinsic vagal tone to the airways. They also block reflex bronchoconstriction caused by inhaled irritants. These agents lost favor because of the length of time for onset of action and because of local and systemic adverse effects that could produce drying of respiratory secretions, blurred vision, and cardiac and central nervous system stimulation. Although atropine is the prototype anticholinergic agent, it is used infrequently because it is readily absorbed from the respiratory and gastrointestinal tracts and is associated with unwanted systemic adverse effects. Atropine should not be used in patients with narrow-angle glaucoma or prostatic hypertrophy.

The development of the quaternary derivative ipratropium has stimulated new interest in anticholinergic therapy.[50] Ipratropium has very low bioavailability when inhaled and hence lacks atropine's side effects. Ipratropium has been shown to be effective during status asthmaticus when used in nebulized form in combination with adrenergics.[51,52] In children, ipratropium has bronchodilator action in acute exacerbations of asthma. However, the benefits of its use in day-to-day management of asthma in children and adults have not been established.

The regular use of anticholinergics as bronchodilators appears to be most effective in patients with chronic obstructive pulmonary disease and partially reversible airflow obstruction.[53]

Aerosol Therapy

All aerosolized medications that are used to treat asthma are available as metered-dose inhalers (MDI).[54] The advantage of delivering drugs directly into the airways is that high concentrations of drug can be delivered to the airways, while systemic side effects are usually avoided. The major disadvantage of this mode of drug delivery is that training and skill are required to coordinate activation of the metered-dose inhaler with inhalation of the drug. This has led to renewed attention to the teaching of proper MDI technique and to the development of a large number of devices known as spacers or chambers, designed to facilitate delivery of the aerosol to the pulmonary airways.

Patients should be instructed in the use of a metered-dose inhaler, and their technique should be checked periodically (see Chapter 5, Patient Education). For the patient who uses the metered-dose inhaler incorrectly, a spacer improves bronchodilator effectiveness. Spacer devices allow discharge of the drug in the MDI into a chamber where particles of medication are held in suspension for 3-5 seconds. During this time, the patient can inhale the drug. Spacers eliminate the rapid initial particle velocity, reducing the irritant properties of the aerosol and the tendency to cough. They also reduce deposition in the mouth and oropharynx, decreasing cough as well as the possibility of oral candidiasis when used to deliver steroids. Spacer devices are indicated principally in the young patient, in those patients who have coordination problems that prevent the correct use of the metered-dose inhaler, and in patients who have particularly irritable airways. A device that combines a face mask with a spacer may also decrease the age at which metered-dose inhalers can be used, although data evaluating this device are limited.

More recently, devices activated by the patient's inhalation have become available, as have dry powder inhalers that do not utilize freon propellants.[55] These devices have similar potency to standard metered-dose inhalers. Dry powder inhalers require an inhalation technique that is different from the MDI technique. Patients need to be carefully instructed (see Chapter 5, Patient Education).

Nebulized or "wet" aerosols generated by an air compressor are particularly useful for children under 5 years of age and in the treatment of severe asthma where respiratory insufficiency could impair inhalation from a metered-dose inhaler or dry powder inhaler.[56]

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5
Patient Education

Health education by the clinician is a powerful tool for helping patients gain the motivation and skill to control their asthma.[1,2] The strategies and suggestions in this chapter are options to be used by anyone educating the patient or family about asthma, including clinicians (physicians and nurses), health educators, community groups, teachers, and social workers.

Patient education should begin at the time of diagnosis and be integrated with continuing care. Each office visit, however brief, should be viewed as an opportunity for patient and family education. The essentials of patient education can be covered by the busy clinician over a series of visits. All members of the health care team should participate in this process. The educational needs of patients and family members can change over time and therefore should be reassessed at regular intervals.

Establishing A Partnership

Much of the day-to-day responsibility for managing asthma falls on the patient and the patient's family. Encouraging active participation in a partnership with the clinician can improve patient adherence to the treatment plan and stimulate family effort to improve control of the patient's asthma.[3,4] The concept of a partnership includes open communication, joint development of a treatment plan by the clinician and patient, and encouragement of the family's efforts to improve prevention and treatment of symptoms. Patients need continuing care from a clinician who is motivated to care for people with asthma. The medical treatment plan needs to be flexible and adaptable to meet changing needs. The patient and the family should be encouraged to assume a significant role in decision-making about actions needed to control symptoms, including changes in the dose or frequency of prescribed medications.

Initial points to cover in establishing a clinician/patient/family partnership include:

- The nature of the proposed partnership and the patient's agreement to it.
- The goal of treatment, i.e., to enable the patient to take part in all normal activities without incurring symptoms.
- The chronic nature of asthma.
- Patient or family questions and fears about asthma.

Patient education involves helping patients understand asthma, learn and practice skills necessary to manage asthma, and be supported for their efforts. Providing information is necessary, but it is not enough to accomplish these objectives.

Encouraging Adherence to the Treatment Plan

There are a variety of actions the clinician can take to encourage patient adherence to the treatment plan.[5,6]

- Clarifying the patient's expectations for treatment and answering questions. Research shows that patients will be able to focus fully on the clinician's recommendations only after major concerns or fears have been addressed.[7]
- Involving the patient and family in the development of a treatment plan.
- Simplifying the treatment plan where consistent with optimal care.
- Providing the patient with diaries to record antecedents of asthma exacerbations, symptoms, actions taken, outcomes, and peak expiratory flow rates. Diaries improve adherence and increase motivation to control health problems[8] because they help patients see patterns of triggers and symptoms as well as response to therapy. Sample diaries are shown in Figure 5-1a, b, and c.
- Providing written instructions. Figure 5-2 lists points to be included. Figure 5-6 gives instructions on using metered-dose inhalers.
- Explaining how each medication works to control or prevent symptoms.
- Having the patient describe the plan to evaluate his or her understanding of the therapeutic program.
- Determining whether the patient can afford to buy the medications prescribed, and if not, considering alternative therapies or payment methods.
- Evaluating the results of the treatment plan with the patient and providing positive reinforcement for goals achieved.
- Identifying problems with adherence by asking:[9]
  - —What problems do you have with giving or taking the medicine?
  - —When you feel better, do you sometimes stop taking the medicine before the recommended time?
  - —If you feel worse when you take the medicine, do you sometimes stop taking it?

Affirmative answers to these questions indicate a problem in the treatment plan. Discussion with the patient is needed to identify and overcome barriers to adherence or to negotiate changes in the plan.

Patient Education Essentials: The Content of Teaching

Patient education involves helping patients understand asthma, learn and practice the skills necessary to manage asthma, and be supported for adopting appropriate asthma management behaviors. Providing information is necessary, but it is not enough to accomplish these objectives. Teaching of patients should also emphasize the development of both the patient's asthma management skills and the confidence that he or she can control asthma. This includes providing information about asthma, demonstrating asthma management practices (e.g., how to take medicine, how to use a peak flow meter), and having the patient demonstrate his or her skill to the clinician for practice and to receive correction if necessary. Patient education also involves helping patients secure the resources necessary to adhere to the prescribed treatment plan and reinforcing the patient and family for appropriate asthma management practices.

Following are brief outlines of key topics to cover in patient education about asthma. Lay language is suggested under each topic.

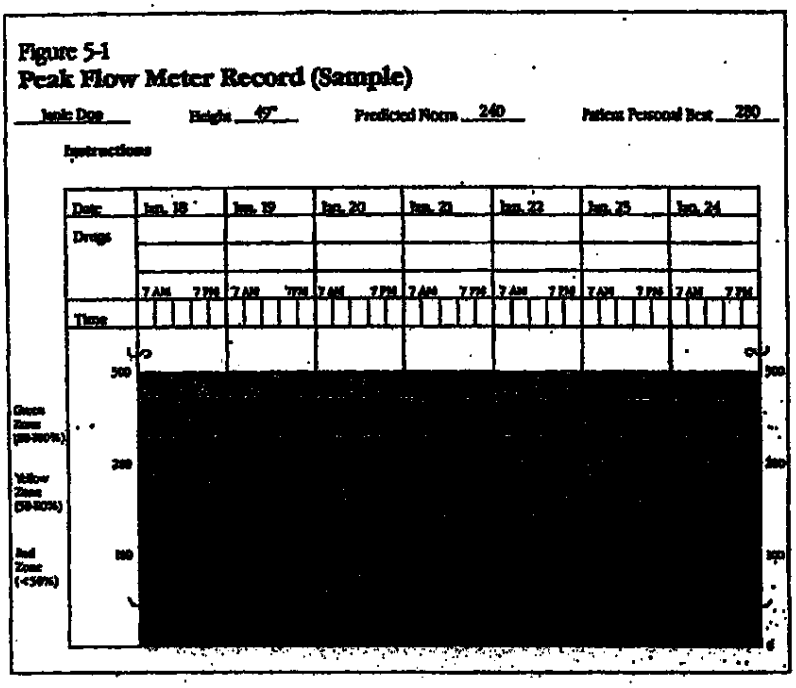
Definition of Asthma

Asthma is a chronic lung disease with the following features: (1) temporary obstruction (blocking) of airflow that leads to breathing difficulty, (2) inflammation (swelling) of the airways, and (3) increased sensitivity of the airways to a variety of triggers that cause breathing difficulty.

Key Points About Signs and Symptoms of Asthma

■ ***The main symptoms of acute asthma episodes*** are shortness of breath, wheezing, tightness in the chest, and/or recurrent cough persisting more than a week.

Figure 5-1
Peak Flow Meter Record (Sample)



■ ***Symptoms vary among patients.*** Not all patients wheeze; persistent cough alone may be the first symptom, especially for young children.

■ ***Recognize and treat even mild symptoms,*** because these symptoms may be early signs of a more serious episode.

■ ***Regular peak flow measurements*** can help detect early signs of asthma episodes before symptoms occur.

Characteristic Changes in the Airways of Asthma Patients and the Role of Medications

■ ***Inflammation*** of the lining of the airways is one of the universal features of asthma. It results from the release of chemicals made by cells in the airway. The airway lining swells and narrows the airways. Inflammation and swelling can persist for weeks after an episode. Medications such as steroids are used to reduce inflammation. Inhaled steroids or cromolyn used regularly may prevent it.

■ ***Bronchospasm*** is caused by tightening of muscles that surround the airways. This response is also a universal feature of asthma and can be reversed quickly by using bronchodilators. If these do not reverse bronchospasm within 15 to 30 minutes, the patient should call the clinician.

■ ***Excessive, thick mucus*** that narrows the airways is often produced during an asthma episode. Steroids may help reduce the production of mucus. When the acute phase of an asthma episode is over, deep coughing may help remove the mucus.

Asthma Triggers and How To Avoid, Eliminate, or Control Them

■ ***Allergens and irritants.*** Environmental control or avoidance of allergens, antigens, and indoor pollutants, including cigarette smoke and occupational exposure, is critical (see Chapter 6, Managing Allergy in the Asthma Patient, for specific allergens and methods of control). Environmental factors can greatly influence the severity of asthma. Treatment is often ineffective unless environmental control measures are also made.

■ ***Viral respiratory tract infections.*** These are common asthma triggers, especially for young children. Parents should be particularly alert for early signs of an acute asthma episode when children have colds or the flu. Starting (or increasing) asthma medications at the first sign of asthma symptoms may stop an episode quickly or keep it from getting severe. It is important to review the medication plan with the clinician before increasing the dose of medication, especially if the child has a fever.

Some children have an established pattern in which their asthma gets bad very quickly every time they get a cold. For these patients, it may be appropriate to start oral corticosteroid treatment at the earliest sign of a cold or the flu rather than waiting for acute asthma symptoms to develop. This treatment should only be started under the supervision of a physician. (See Chapter 7, Management of Asthma.)

Viral respiratory infections may also be a significant trigger for adults with asthma. Adults who have a cold and start to have acute asthma symptoms may need to add or increase anti-inflammatory asthma medication in order to control the asthma symptoms.

■ ***Exercise.*** Exercise without symptoms is an important treatment goal. Symptoms during exercise signal the need to notify the clinician and to consider using medication before exercising. (See Chapter 9, Exercise-Induced Asthma.)

Treatment

■ ***The need for individualized, continuing care.*** Because patients have individual patterns of triggers and varying levels of severity, treatment must be tailored to the individual and monitored by a clinician on a regular basis. Asthma is a chronic illness and requires continuous medical care to control symptoms and prevent acute exacerbations.

■ ***How medications work to relieve and/or prevent symptoms.*** Bronchodilators such as theophylline and beta$_2$-agonist medications relax muscles in the airways, allowing the airway to open fully. Cromolyn sodium helps prevent inflammation of the airways. Corticosteroids both prevent and reduce airway inflammation. It is important to follow recommended timing and dosage of medications in order to achieve the benefits of reduced inflammation, bronchospasm, and mucus production. For example, medications used to treat an acute episode must often be continued for a few days or weeks after the episode to help airway inflammation heal.

■ ***Adverse effects and how to reduce them.*** The patient should be alerted to potential adverse effects. If adverse effects cannot be controlled, the clinician should be contacted. If the clinician cannot be reached immediately, the patient should reduce the dose by half or skip the next dose rather than stop the medication entirely. Some adverse effects are not serious but can be bothersome. Ways to reduce the effects (e.g., taking oral medication with food may reduce gastric upset; rinsing the mouth after taking medicine may reduce thrush) or to reduce the dosage should be discussed with the clinician.

■ ***Preventive treatment.*** It is important to take preventive medicine regularly and consistently. Airway inflammation makes a person with asthma vulnerable to episodes; preventive medicine reduces the inflammation and therefore gives some protection. Even when a person with asthma is not feeling any symptoms, this protection is needed.

■ ***Early treatment.*** The onset of symptoms should be treated within 5 minutes with medication. It is easier and takes less medicine to stop an episode in its early phase than later.

Patient Fears Concerning Medication

■ ***Long-term adverse effects,*** especially with steroids. Widely disseminated information in the news media about anabolic steroids used by athletes has caused many people to fear taking steroids in any form. Patients should be told that inhaled corticosteroids are not like anabolic steroids. Inhaled steroids do not have the muscle and liver effects that anabolic steroids have.

Most people fear that the devastating side effects associated with long-term use of oral corticosteroids will occur regardless of the route or duration of administration. This does not appear to be true. Inhaled corticosteroids in therapeutic doses are poorly absorbed into the bloodstream and cause few adverse effects. Oral thrush and hoarseness sometimes occur, but can be prevented by using a spacer with the medication or by rinsing the mouth after the inhalations are complete. Emphasize the safety of inhaled steroids and the efficacy of topical application directly to the inflamed and irritated airway.

When asthma is very severe, a short course (2 weeks or less) of oral steroids may be needed, but it is also quite safe. The modest adverse effects that might occur are outweighed by enhanced recovery from serious episodes.

Dangerous adverse effects from oral steroids are associated with long-term use only.

- ***Toxicity***, indicated by adverse effects such as shaky hands or legs, rapid heart beat, or vomiting. These side effects are temporary and can be minimized by reducing the dosage.
- ***Addiction***. Asthma medications are not addictive.
- ***Reduced effectiveness with continuous use***. Research studies have not shown this to be the case. If it appears to the patient that effectiveness is reduced, e.g., that the recommended number of uses of the metered-dose inhaler is not sufficient, the severity of the asthma and the therapy may need to be reevaluated.

Use of Written Guidelines

A written plan to follow for all medications and for handling acute episodes will improve adherence and management of episodes. Figure 5-2 lists suggested topics; Figures 5-3, 5-4, and 5-5 present sample plans.

Correct Use of Inhalers

The proper use of inhalers[9,10] is shown in Figure 5-6. Patients should demonstrate use of the metered-dose inhaler (MDI) to the clinician, and the patient's MDI technique should be reviewed at every visit. Describing the efficacy of delivering medication directly to the inflamed airway will encourage patient use of inhalers. When several inhalers are prescribed, label them to reflect the intended use (e.g., prn or regularly scheduled; which inhaler to use first).

Criteria for Premedicating To Prevent Onset of Symptoms

Sometimes situations that trigger asthma episodes cannot be avoided. Premedication with cromolyn sodium or beta$_2$-agonist agents can prevent symptoms from occurring. Patients may require premedication before exercise and before exposure to allergens, cold air, or irritants.

Criteria for Detecting the Onset of Symptoms and Initiating Treatment

Recognizing early warning signs or symptoms of airflow obstruction will enable patients to begin treatment immediately. Early warning signs vary among individuals but generally include:

- Peak flow level 20 percent below predicted or personal best level.
- Cough or wheeze, particularly during daily activities.
- An individual pattern of early signs such as tightness of the chest, shortness of breath, or dark circles under the eyes in children.

Indications for Emergency Care

The following signs require immediate emergency medical care:

- Cyanosis (gray or blue fingernails or lips).
- Difficulty breathing, walking, or talking.
- Retractions of the neck, chest, or ribs; nasal flaring.
- Failure of medications to control worsening symptoms.
- Peak expiratory flow rate either declining steadily after each treatment or falling below 50 percent of predicted or personal best level.

Optimal Use of Home Peak Expiratory Flow Rate Monitoring

Home peak expiratory flow rate (PEFR) monitoring is helpful for people with moderate or severe asthma (see Chapter 2, Objective Measures of Lung Function). The patient and clinician use peak expiratory flow rate monitoring to help make decisions about when to initiate or terminate treatment or to seek emergency care. Daily measures will help identify patterns of airway obstruction that may indicate a need for additional treatment. For example:

Figure 5-2
Written Guidelines for Patients and Families

Written guidelines should include the following points:

- Specific instructions about use of medications, including dose, frequency of administration, guidelines for changing dose or adding medications if appropriate, and about adverse effects to report to the clinician.
- How to monitor body signs or symptoms and/or peak expiratory flow rate (PEFR) to detect increasing airflow obstruction as early as possible; early signs of airflow obstruction vary according to the individual and should be identified for each patient.
- Criteria for initiating or modifying treatment: a drop in PEFR or early signs or symptoms.
- List of steps to take in managing an acute asthma episode (i.e., removing the precipitating trigger, giving medication, avoiding strenuous physical activity, and keeping patient and family calm).
- Specific criteria for seeking emergency medical care, including a pattern of declining PEFR, failure of medications at home to control worsening symptoms; difficulty in breathing (wheeze may be absent), walking, or talking; intercostal retractions; blue fingernails or lips.
- Observable signs that long-term therapy is less than optimal, such as sleep interruption and/or consistently low or highly variable PEFR. Such signs should be discussed with the clinician.

■ ***Decrease in PEFR*** from predicted or personal best level suggests onset of asthma episode.

■ ***High variability*** in PEFR readings is a sign of increased airway hyperresponsiveness and usually suggests the need for anti-inflammatory medications.

■ ***Evening dips below morning PEFR levels*** may indicate the need to change the dose or timing of medications.

■ ***Sudden episodes of breathlessness.*** PEFR measurements can determine whether air flow obstruction is present. If the value remains within the patient's normal range, the breathlessness may be due to panic or anxiety, in which case relaxation strategies may be useful.

Fears and Misconceptions

Many patients and families have fears about asthma that cause distress and may prevent adherence to the treatment plan. Identifying and dealing with fears and misconceptions not only will improve adherence but will also help the patient and family live with asthma without undue stress. Fears and misconceptions may concern:

■ ***Cause of asthma.*** Emphasize that asthma is not caused by psychological factors.

■ ***Asthma fatalities.*** Most deaths are related to undertreatment (i.e., poor long-term treatment and poor management of acute episodes) and are rare in children.

■ ***Physical activity limitations.*** People with asthma should live full and active lives. Exercise without symptoms is a realistic treatment goal.

Figure 5-3
Sample Action Plan for Asthma Episodes: Adults

Assess severity of the episode by rating the severity of symptoms and/or measuring peak flow.

Mild Episode

Symptoms:	Mild wheeze, cough, chest tightness, shortness of breath occurring with activity but not at rest.
Peak flow:	70-90% of baseline (personal best or predicted, as determined by the clinician).
Actions:	Take inhaled bronchodilator. If improved, continue medication on regular basis for 24-48 hours. If not improved, take action as indicated for moderate episode.

Moderate Episode

Symptoms:	Wheeze, cough, chest tightness, and shortness of breath while at rest; symptoms may interfere with daily activity.
Peak flow:	50-70% of baseline.
Actions:	Repeat inhaled bronchodilator every 20 minutes for 1 hour. If improved, continue medication every 3-4 hours for 24-48 hours. If not improved in 2-6 hours after initial treatment, begin or increase prednisone. Contact your clinician.

Severe Episode

Symptoms:	Severe shortness of breath, wheeze (wheeze may disappear with very severe episode), cough, and chest tightness at rest; difficulty walking and talking; perhaps retraction of muscles in chest or neck.
Peak flow:	Less than 50% of baseline and little response to bronchodilator.
Actions:	Repeat inhaled bronchodilator, 4-6 puffs, every 10 minutes up to three times. Begin or increase prednisone. Contact your clinician if available. **If there is no significant improvement after 20-30 minutes, seek emergency care immediately.**

BE PREPARED:
Have a plan for getting to emergency care quickly in the event of a sudden episode. Keep emergency phone numbers handy. Always carry an inhaler of bronchodilator medication with you.

■ ***Prognosis.*** With proper treatment, asthma does not lead to permanent lung disability.

Figure 5-7 reproduces a fact sheet from the National Asthma Education Program illustrating ways to address such misconceptions.

Family Understanding and Support

Decisions about the patient's treatment or activities often affect other family members.[4] Family conflict is common when members misunderstand or disagree about the cause, treatment, or prognosis for asthma. Likewise, misconceptions about asthma can limit patient participation in school and work activities. Educating the family and other people who play a significant role in the patient's life (e.g., teachers, supervisors) can help resolve such problems by increasing support for patient adherence to the treatment plan and helping the patient develop a positive attitude toward managing asthma. It is particularly important to identify a person in the family or a friend who can help the patient follow the written plan for managing an acute episode.

Communication With the Child's School

School personnel are often frightened of asthma episodes and are rarely well prepared to cope with them. As a result, children sometimes are barred from sports or from taking medications at school.

■ Parents should communicate with classroom and physical education teachers, the school nurse, and the principal about the child's asthma.

■ A written statement for school personnel will guide decisions about the child's participation in activities as well as about managing acute episodes at school. The letter should include a brief description of the patient's condition and guidelines for responding to symptoms of asthma. Figure 5-8 provides a sample letter from the clinician to school personnel.

Feelings About Asthma

School-age children and young adults may have difficulty accepting that they have asthma. Poor self-image and feelings of social stigma are common. Adherence to the treatment plan can require difficult compromises in lifestyles, and unpredictable episodes can be embarrassing and difficult to manage. Life-threatening episodes may cause incapacitating fear and feelings of helplessness. In addition, feelings of dependency and loss of self-esteem may stem from the need for constant medication. Discussing feelings about asthma with the clinician will help patients:

■ Acknowledge the validity of these feelings.

■ Provide strategies for controlling asthma.

■ Take responsibility for managing their asthma and to live as normally as possible.

■ Obtain referrals to group self-management programs, support groups, and asthma camps.

■ Obtain referrals for psychological counseling. This is important for patients who become seriously depressed because depression has been identified as a risk factor for fatal asthma.[5]

■ Obtain referrals for social services, psychologists, or counselors of cultural and economic background similar to that of the patient when there are social, psychological, cultural, or attitudinal barriers to good self-management behavior change that cannot be resolved by the clinicians.

Additional Educational Resources

Although the primary responsibility for health education is the clinician's, group education may serve as a supplement.

A number of programs to educate families about the management of childhood asthma have been developed and evaluated.[16,17] Results include increased family skill in managing asthma at home, improved quality of life, and reduced school absences, morbidity, and emergency use of health care services.[16,17]

Materials and guidelines[2,3,4,10,12] for individual or group education and support networks are available through a variety of professional and voluntary organizations. A complete listing of resources is available from the National Asthma Education Program.

Figure 5-1a.
Weekly Asthma Symptom and Peak Flow Diary

Date	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Peak flow														
No symptoms														
Mild														
Moderate														
Severe														

Measure your peak flow reading every morning (a.m.) on wakening and every evening (p.m.) at bedtime before taking inhaled medications. Write down the highest reading of three tries in the box for peak flow.

In the space below the date and time, put an X in the box that matches the symptoms you have when you record your peak flow reading. If you are taking asthma medicine, put a circle around the X like this (X). If you take more or less medicine than usual, please make a note.

No symptoms = No symptoms (wheeze, cough, chest tightness, or shortness of breath) even with normal physical activity.

Mild symptoms = Symptoms during physical activity, but not at rest.

Moderate symptoms = Symptoms while at rest; symptoms may interfere with daily activity.

Severe symptoms = Severe symptoms at rest (wheeze may be absent); symptoms cause difficulty walking or talking; retraction of muscles in neck or between ribs when breathing.

Figure 5-1b.
Peak Flow Meter Record

_____ Height _____ Predicted Norm _____ Patient Personal Best _____

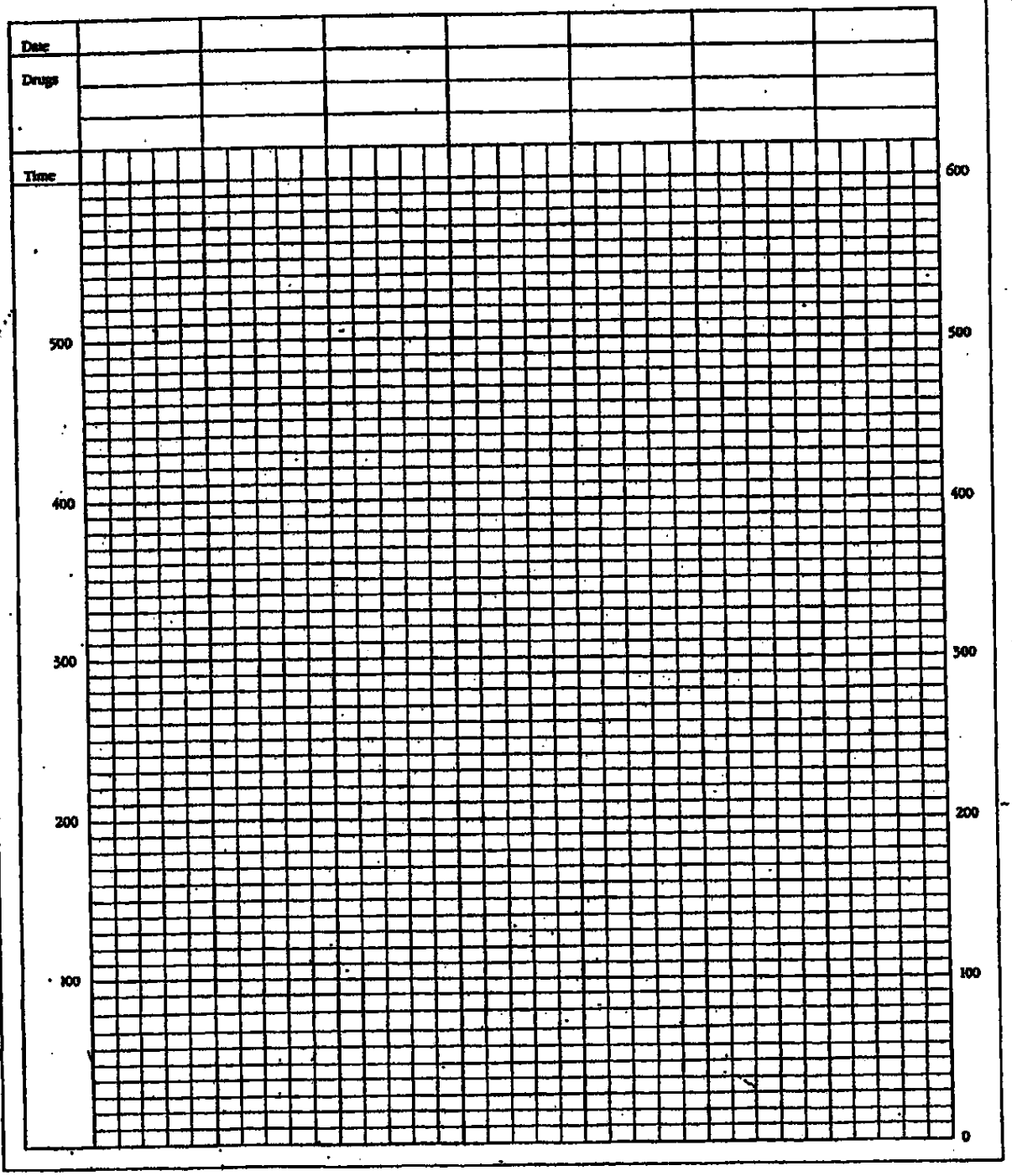


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Figure 5-4

Family Guide for Managing a Child's Asthma Episode

Steps To Manage an Asthma Episode at Home

- Know your child's early warning signs so you can begin treatment early.
- Give the prescribed amount of medicine at the times or intervals the doctor has indicated. If your treatment plan includes increased dosage or a second medicine to be used during episodes, give it as instructed. If you need to give more medicine than prescribed, notify your clinician.
- Remove, if possible, an allergen or irritant if one or the other triggered the child's episode. Treatment is less effective if there is continued exposure to a trigger.
- Keep yourself and your child calm and relaxed.
- Have your child rest while you observe the progress of therapy.
- To monitor your child's condition, note change in body signs like posture, difficulty breathing, wheeze, and cough. If you have a peak flow meter, test the child's peak flow rate 5-10 minutes after each treatment to see if airflow is returning to normal.
- Call a family member, friend, or neighbor to help you if needed.
- Call the clinic, doctor's office, or hospital for help if needed.

Signs To Seek Medical Care

Not all asthma episodes require a visit to the doctor. There are several signs that parents can use to decide if a trip to the doctor or emergency department is needed. If any one of these signs is present, seek emergency treatment for your child.

- Wheeze, cough, or shortness of breath gets progressively worse, even after the medicine has been given and had time to work. Most inhaled bronchodilator medications produce a noticeable and significant effect within 5-10 minutes. Discuss the time your child's medications take to work with your doctor.
- Peak flow rate declines or stays the same following treatment with bronchodilators or drops to 50% or less of the child's normal baseline level (personal best or predicted; as determined by the clinician). Discuss this peak flow level with your doctor.
- Child has a hard time breathing. Signs of this are:
  - —Child's chest and neck are pulled or sucked in with each breath.
  - —Child is hunched over.
  - —Child is struggling to breathe.
- Child has trouble walking or talking.
- Child stops playing and cannot start any activity again.
- Child's lips or fingernails are grey or blue. If this happens, take your child to the doctor or emergency room IMMEDIATELY!

Figure 5-5
Patient Guide for Management of Asthma: Adults

Know your own pattern of asthma symptom episodes; recognize your own early warning signs.

Evaluate severity of episodes by rating how short of breath you feel on a scale of 1 to 10. Consider how much your activity is limited.

Keep a record of your peak flow. Measure peak flow at least daily, in the early morning upon arising before medications. Know your normal peak flow when you are free of symptoms. Learn to recognize an altered pattern and how far you have deviated from your normal peak flow. If peak flow drops in a.m. by 20% compared to previous days, begin treatment with bronchodilators and evaluate results of treatment.

Learn what triggers your asthma by keeping a diary and consulting with your clinician. Take steps to avoid, eliminate, or control these triggers. Environmental control measures may prevent or minimize the severity of asthma episodes.

Identify and assign priorities to strategies that work for you to reduce the intensity and distress of symptoms. Use them in the order that works best for you. Keep a journal or diary of severe episodes. List the strategies you tried and how effective they were.

Plan ahead. Before going into a new situation, think what you will do if you develop asthma symptoms. Keep resources and inhalers handy. Don't get caught without your medicine and other resources that help you get through a situation.

Have a crisis plan. Know what you will do in the event of a severe episode that does not get better with medications that you carry with you. Know how to get to medical help quickly, including how and when to call an ambulance. Have a partner or friend that you can call for help to get to the emergency room or the clinic quickly—but don't let things get this bad.

If you experience panic attacks, check your peak flow to be sure it is in your normal range. Simple relaxation or meditation strategies may relax you and permit slower, deeper breathing, thus allowing a sense of control over breathing.

Get the information you need to cope with asthma by forming a partnership in self-management with your clinician. Prepare a list of questions you want answered before you go to your clinic appointments. Ask for resources and help including phone numbers to use when you need advice and support. Ask your doctor what the prescribed medications are supposed to do for you and what you can reasonably expect.

Develop a partnership with a friend who knows your asthma well, knows what coping strategies work for you, and can help you and be a source of support.

Sleep disruption or exercise intolerance indicates your treatment is less than optimal. See your clinician.

Figure 5-6
Correct Use of a Metered-Dose Inhaler*

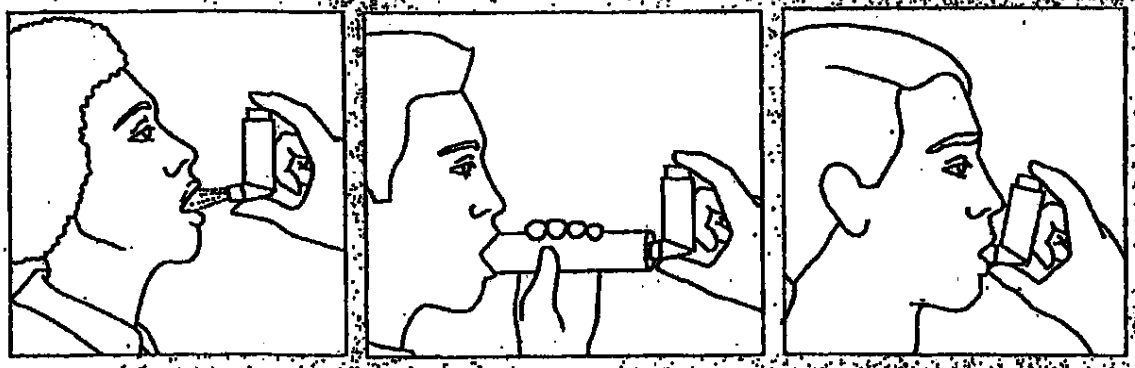
Steps for checking how much medicine is in the canister

1. If the canister is new, it is full.
2. If the canister has been used repeatedly, it might be empty. (Check product label to see how many inhalations should be in each canister.)

   To check how much medicine is left in the canister, put the canister (not the mouthpiece) in a cup of water.
   —If the canister sinks to the bottom, it is full.
   —If the canister floats sideways on the surface, it is empty.

Steps for using the inhaler

1. Remove the cap and hold inhaler upright.
2. Shake the inhaler.
3. Tilt the head back slightly and breathe out.
4. Position the inhaler in one of the following ways (A is optimal, but C is acceptable for those who have difficulty with A or B):



A. Open mouth with inhaler 1-2 inches away.

B. Use spacer (this is recommended especially for young children).

C. In the mouth.

5. Press down on inhaler to release medication as you start to breathe in slowly.
6. Breathe in deeply [illegible]
7. *Hold* breath for 10 seconds to allow medication to reach deep into lungs.
8. Repeat puffs as directed. Waiting [illegible] between puffs may help [illegible]
9. Spacers are used for all [illegible] with inhaled steroids.

*Note: Inhaled drug [illegible] around the [illegible]

Check Your Asthma "I.Q."

National Asthma Education Program

Prepared by the National Heart, Lung, and Blood Institute

The following true-or-false statements test what you know about asthma. Be sure to read the correct answers and explanations on the back of this sheet.

	True	False
1. Asthma is a common disease among children and adults in the United States.	☐	☐
2. Asthma is an emotional or psychological illness.	☐	☐
3. The way that parents raise their children can cause asthma.	☐	☐
4. Asthma episodes may cause breathing problems, but these episodes are not really harmful or dangerous.	☐	☐
5. Asthma episodes usually occur suddenly without warning.	☐	☐
6. Many different things can bring on an asthma episode.	☐	☐
7. Asthma cannot be cured, but it can be controlled.	☐	☐
8. There are different types of medicine to control asthma.	☐	☐
9. People with asthma have no way to monitor how well their lungs are functioning.	☐	☐
10. Both children and adults can have asthma.	☐	☐
11. Tobacco smoke can make an asthma episode worse.	☐	☐
12. People with asthma should not exercise.	☐	☐

Your Score—How many answers did you get correct?

11-12 correct	=	Congratulations! You know a lot about asthma. Share this information with your family and friends.
10-11 correct	=	Very good.
Fewer than 10 correct	=	Go over the answers and try to learn more about asthma.

(continued)

Answers to the Asthma "Lung" Quiz

1. **TRUE.** Asthma is a problem that affects young children and adults in the United States and it is increasing. About 10 million people have asthma, of whom 3 million are under 18 years of age.

2. **FALSE.** Asthma is not an emotional or psychological disease, although strong emotions can sometimes make asthma worse. People with asthma have sensitive lungs that react to certain things, causing the airways to tighten, swell, and fill with mucus. The person then has trouble breathing and may cough and wheeze.

3. **FALSE.** The way parents raise their children does not cause asthma. It is not caused by a poor parent-child relationship or by being overprotective.

4. **FALSE.** Asthma episodes can be very harmful. People can get very sick and need hospitalization. Some people have died from asthma episodes. Frequent asthma episodes, even if they are mild, may cause people to stop being active and living normal lives.

5. **FALSE.** Sometimes an asthma episode may come on quite quickly. However, before a person has any wheezing or shortness of breath there are usually symptoms such as a cough, a scratchy throat, or tightness in the chest. Most patients learn to recognize these early symptoms and can take medicine to prevent a serious episode.

6. **TRUE.** For most people with asthma, an episode can start from many different "triggers." Some of these things are pollen from trees or grasses; molds or house dust; weather changes; strong odors; cigarette smoke; and certain foods. Other triggers include being upset; laughing or crying hard; having a cold or the flu; or being near furry or feathered animals. Each person with asthma has an individual set of asthma "triggers."

7. **TRUE.** There is no cure yet for asthma. However, asthma patients can control it to a large degree by:
   - Getting advice from a doctor who treats asthma patients
   - Learning to notice early signs of an asthma episode and to start treatment
   - Avoiding things that cause asthma episodes
   - Taking medicine just as the doctor says
   - Knowing when to get medical help with a severe episode.

8. **TRUE.** Several types of medicines are available to control asthma. Some people with mild asthma need to take medication only when they have symptoms. But most people need to take medicine every day to prevent symptoms and also to take medicine when symptoms do occur. A doctor needs to decide the best type of medicine for each patient and how often it should be taken. Asthma patients and their doctors need to work together to manage the disease.

9. **FALSE.** People with asthma can monitor how well their lungs are functioning with a peak flow meter. This small device can be used at home, work, or school. The peak flow meter may show that the asthma is getting worse before the usual symptoms appear.

10. **TRUE.** Both children and adults can have asthma. Sometimes, but not always, symptoms will go away as children get older. However, many children continue to have asthma symptoms throughout adulthood. In some cases, symptoms of asthma are not recognized until a person is an adult.

11. **TRUE.** Smoke from cigarettes, cigars and pipes can bring on an asthma attack. Indoor smoky air from fireplaces and outdoor smog can make asthma worse. Some can also "set off" other triggers. Smokers should be asked not to smoke near someone with asthma. Moving to another room may help, but smoke travels from room to room. No smoking is best for everyone!

12. **FALSE.** Exercise is good for most people—with or without asthma. When asthma is under good control, people with asthma are able to play most sports. For people whose asthma is brought on by exercise, medicines can be taken before exercising to help avoid an episode. A number of Olympic medalists have asthma.

For more information on asthma, write:
National Asthma Education Program
4733 Bethesda Avenue, Suite 530
Bethesda, MD 20814-4820

National Asthma Education Program
Coordinated by the Office of Prevention, Education, and Control
National Heart, Lung, and Blood Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
NIH Publication No. 90-1128
January 1990

Figure 5-8
Sample Letter from Clinician to School Personnel

Information on Asthma for Teachers

Name: _____

is participating in an asthma self-management program. This student is working with us to help take care of her or his asthma. The following guidelines will help you maximize the student's participation in all school activities.

- Full participation in all physical activities to the limits of tolerance is essential to health. The student should be allowed to rest if necessary during this physical exertion and use inhaled medications as needed.
- Medication is important in the treatment of asthma. The student must take medicine by the following schedule:
  a. _____ (time) every day.
  b. as needed if symptoms of coughing, wheezing, congestion, or chest tightness occur.

  Your cooperation in this medication schedule will help prevent any asthma problems. Please allow this child to keep asthma medications with him or her to use as needed or directed.
- If asthma symptoms come on during school or gym activities, inhaled medication and rest will help to control the symptoms. This student knows the early warning signs that tell him or her to stop and to rest and use inhaled medication as needed.
- Some children may have a peak flow meter with them and know what readings indicate worsening asthma. Use this information to guide decisions. Remember: higher readings mean the airway is opening and asthma is getting better. Lower readings mean the airway is tightening and asthma is getting worse.
- If symptoms get worse or don't improve [illegible] minutes after medicine is taken, [illegible] family should be notified.

If you have further questions about this student's asthma, please call the doctor:

_____ (name)

at _____ (phone)

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6
Managing Allergy in the Asthma Patient

Allergy has a significant role in the pathophysiology of asthma (see Chapter 1, Definition and Diagnosis). This chapter discusses two interventions that contribute to the management of allergy in asthma patients: (1) environmental control measures to reduce exposure to allergens and irritants and (2) immunotherapy.

Environmental Control Measures

Environmental control to reduce exposure to indoor and outdoor allergens is a critical component of asthma management. Major allergens and control measures are discussed in this section.

Avoid Outdoor Allergens

Exposure to outdoor allergens is best reduced by remaining indoors, preferably in an air conditioned environment,[1,2] particularly during the midday and afternoon when pollen and some mold spore counts are highest.

■ ***Pollens.*** Particles greater than 10 microns in diameter are usually cleared in the nose and mouth and do not generally penetrate the lower airway.[3] However, some plants produce allergen-containing particles that are less than 10 microns.[4,5] Asthma associated with ragweed[6] and grass[7] pollination has been clearly documented.

■ ***Molds.*** Mold spores are generally smaller than pollen grains and are more likely to penetrate the lower airway. Mold spores exist primarily out of doors and tend to be seasonal. Some fungi sporulate on warm, dry summer days; others prefer the rainy nights of fall.[8] Keeping windows closed during seasons of high mold production will reduce exposure.

Eliminate Indoor Allergens

Environmental control to reduce exposure to indoor allergens is a critical component of asthma management.

■ ***House dust.*** Many indoor allergens are components of house dust. There is no evidence that house dust itself is an allergen. However, there are allergic components in house dust; the most important include animal dander, mites, and cockroach allergen.[9] These can be controlled by the following methods:

—*Animal allergens.* Dogs are found in an estimated 43 percent of American homes, cats in 28 percent, and pet rodents were present in 2 percent.[10] Dander from these animals contributes greatly to the allergenic composition of house dust.[9] All warm-blooded pets can cause allergic reactions, including small rodents and birds. Furthermore, products made from feathers retain the allergen from the bird. All breeds of cats produce common allergens, and cat saliva and cat dander are potent allergens. Dogs also produce a common allergen, although minor breed differences exist. There is no "nonallergenic" dog; short-haired dogs are just as allergenic as those with longer hair.

Environmental control to reduce exposure to indoor and outdoor allergens is critical. It can reduce asthma symptoms, the need for medication, and the level of airway hyperresponsiveness.

To eliminate exposure to animal dander, the animal should be removed from the house. Removal of the pet may not afford immediate relief even when followed by vigorous cleaning, since allergen has been shown to remain in the home for many months.[11] Recent studies indicate that the residual allergen can be denatured and rendered nonallergenic by application of 3 percent tannic acid solution, which is commercially available. If the pet cannot be removed from the house, it should at the very least be kept out of the allergic person's bedroom at all times. If the animal is in the bedroom at all, the dander and saliva will remain long after the pet has left the bedroom. If there is forced-air heating in a home with a pet, the air ducts into the bedroom should be sealed. An electric baseboard heater can be used if necessary. Weekly washing of the pet may reduce the amount of dander and dried saliva deposited on carpets and furnishings.

—*House-dust mites.* House-dust mites appear to have a major role in the causation of allergic asthma.[12] They occur in environments with sufficient humidity since they are quite dependent for survival on moisture from the atmosphere. Mite antigen is found throughout the home, wherever human dander, the food for the mite, is found. High levels have been reported in dust obtained from mattresses, pillows, carpets, upholstered furniture, bed covers, clothes, and soft toys.[13] The principal allergen of the house-dust mite is found in its feces.[9] A gram of dust may contain 1,000 mites and 250,000 fecal pellets. These fecal pellets are quite large (10-40 microns), similar in size to pollen grains. They therefore share some of the aerodynamic features of pollen in that they do not easily enter the lower airway and are rapidly cleared from the air by gravity. Mite antigen is easily demonstrated in the air during housecleaning activities,

but it is present in only very small amounts in undisturbed air.[13] Some mite allergen is associated with smaller size particles that may be in the respirable range for the lower airway.[14]

Elimination of mite exposure is very effective not only in reducing symptoms and the need for medication but also in reducing the level of nonspecific bronchial hyperresponsiveness.[15,16] Figure 6-1 summarizes house-dust mite control measures.

—*Cockroach allergen.* The cockroach also appears to be of importance, particularly in warmer climates and in inner-city neighborhoods in cooler climates.[17] Appropriate roach control methods will benefit the patient.

■ ***Indoor Molds.*** Indoor molds are particularly prominent in environments with increased humidity.[18]

—*Bathrooms, kitchens, and basements.* These areas require adequate ventilation and frequent cleaning using chlorine bleach if necessary. Dehumidifiers for damp basement areas should be considered, with the humidity level set for less than 50 percent but above 25 percent. The unit should be emptied and cleaned regularly.

—*Perspiration.* Perspiration on foam pillows may encourage mold growth. Pillows should be encased or changed every year.

Consider the following when giving advice on controlling indoor allergens:

■ ***Vacuum cleaners.*** These cleaning tools are particularly prone to mobilize fine respirable allergen particles. Allergic patients should preferably not vacuum or, alternatively, should employ a dust mask, a central vacuum cleaner with the collecting bag outside the home, or a vacuum cleaner fitted with a HEPA (high-efficiency particulate air) filter.

Figure 6-1
House-Dust Mite Control Measures

Essential:

- Encase the mattress in an airtight cover.
- Either encase the pillow or wash it weekly.
- Wash the bedding in water of 130°F weekly.
- Avoid sleeping or lying on upholstered furniture.
- Remove carpets that are laid on concrete.

Desirable:

- Reduce indoor humidity to less than 50%.
- Remove carpets from the bedroom.
- Use chemical agents to kill mites or to alter the mite antigens in the house.

■ ***Air conditioning.*** This type of climate control is beneficial, both because it allows windows and doors to remain closed and because it reduces indoor humidity, discouraging mold and mite growth.[19]

■ ***Humidifiers.*** These have a potential for harm. If not cleaned properly and frequently, they can harbor and aerosolize mold spores.[20] Even if they do not directly contribute mold spores, the increased humidity that they produce may encourage growth of both mold[18] and house-dust mites.[21]

■ ***Indoor air-cleaning devices.*** Controlling the source of allergens through environmental control measures is the most important method of reducing indoor allergens, particularly animal dander. However, a number of devices are available for cleaning allergens from the indoor air.[22] Two major categories of air cleaning devices are available:

—Mechanical filters, of which the most effective form is the HEPA filter.

—Electrical filters, of which the most effective form is the electrostatic precipitator. These require frequent cleaning of the plates to keep them working efficiently, and if not well maintained, they produce some ozone.

These filters may be placed within the ducts of a central forced air heating and cooling system, or they may be placed within a room as free-standing units.

In deciding on either kind of filter, several factors should be considered. One is capacity to clean and circulate a significant amount of clean air. This clean air delivery rate can usually be obtained from the manufacturer. A second consideration is the aeroallergens to which the patient is sensitive, and whether they are present in the air in the home in quantities significant enough to make the investment worthwhile and beneficial. Certain allergen components of indoor air are more likely to remain airborne than others (see Figure 6-2).

Avoid Indoor Irritants

There are components of indoor air other than allergens that may be harmful to the asthma patient and should be avoided.

■ ***Tobacco smoke.*** Although not an allergen, tobacco smoke has been shown to have harmful effects on those passively exposed and should not be in the environment of the person with asthma. An increased incidence of asthma has been reported in children who live in a home where the mother smokes.[23] In addition,

children with asthma who are exposed to maternal smoking have been shown to have poorer pulmonary function, a higher requirement for medication especially during the winter months, and more frequent emergency department visits.[24,25] Unlike some aeroallergens, tobacco smoke consists of very small particles that tend to remain airborne for long periods.

■ ***Wood smoke.*** Although smoke from wood-burning heating stoves is not an allergen, it has been reported to increase lower respiratory symptoms in children.[26,27]

■ ***Strong odors or sprays.*** Produced by cosmetics (e.g., perfume, talcum powder), room deodorizers, cooking (especially frying), household cleaning products, and fresh paint, these may irritate some patients' airways and trigger asthma symptoms. Those affected by such odors should avoid them.

■ ***Air pollutants.*** Exposure to oxidants such as ozone and sulfur oxide has been associated with worsening pulmonary function and increased airway hyperresponsiveness in people with asthma. These environmental exposures may interact with allergens and other triggers in the pathogenesis of clinical asthma.

The Role of Immunotherapy in the Treatment of Asthma

Allergen avoidance is always the first recommendation for managing asthma symptoms. However, when avoidance is not possible and appropriate medication fails to control symptoms of allergic asthma, referral for allergy immunotherapy should be considered.

Allergy immunotherapy has been shown to reduce the symptoms of asthma in a number of double-blind studies with a variety of allergens, including house-dust,[28] cat dander,[29] grass pollen,[7] and alternaria.[30] In each of these studies, symptoms of asthma were reduced following injections of the natural allergen. In addition, all studies (except one, in which it was not examined) showed decreased threshold of the skin or lungs to the allergen employed. Furthermore, recent studies have shown that allergen immunotherapy reduces the late reaction to allergen in the lungs.[31] This suggests that allergen immunotherapy can be employed to prevent the development of allergic inflammation and perhaps the resulting bronchial hyperresponsiveness.[6] Indeed, long-term immunotherapy with cat extract has been shown to reduce bronchial responsiveness to challenge with both cat extract and histamine.[32]

The double-blind studies that have demonstrated efficacy of immunotherapy in asthma have been conducted in both children and adults. There is one study indicating that the response to allergy immunotherapy decreases with age and with lower baseline levels of pulmonary function.[33] Although scientific data are lacking to specify the timing of treatment or length of time that immunotherapy should be continued, it is recommended that once patients have achieved maintenance levels of immunotherapy, the interval between injections should be extended, with a goal of monthly injections. If the patient's symptoms improve, treatment is usually continued for 3-5 years, although under some circumstances more prolonged therapy at monthly intervals may be warranted. If there is no evidence of response following two allergy seasons after reaching the maintenance or the highest level tolerated by the patient, immunotherapy should be discontinued. Allergy immunotherapy should only be administered in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can (but rarely does) occur.

Figure 6-2
Relative Likelihood of Indoor Air Components Remaining Airborne

Component	Likelihood of Remaining Airborne in Indoor Environment
Pollens	0 (least likelihood)
Outdoor mold spores	+
Mite allergens	+
Animal allergens	++
Indoor mold spores	++
Tobacco and wood smoke	+++ (greatest likelihood)

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7
Management of Asthma

Asthma is a chronic condition with acute exacerbations. Management requires a continuous care approach to control symptoms, prevent exacerbations, and reduce chronic airway inflammation. This chapter discusses the overall management of asthma as a chronic illness. Chapter 8 discusses management of acute exacerbations.

General principles of therapy are presented, followed by protocols for managing asthma in adults and in children.

A general approach to therapy is outlined in the management protocols and accompanying flow charts. Discussions of considerations that may guide development of individual treatment plans are also included.

General Principles

Treating the Underlying Pathology of Asthma

The overall goals of asthma therapy are (1) to provide symptomatic control of asthma with normalization of lifestyle and (2) to return pulmonary function as close to normal as possible. Figure 7-1 summarizes the goals of therapy. The aim of asthma therapy is to treat the underlying pathology of the condition: therapy should not merely alleviate symptoms but also prevent exacerbations and control chronic symptoms by reducing inflammation. Airway hyperresponsiveness is a major characteristic of asthma and may determine patients' symptoms, disease severity, and possibly mortality. Furthermore, because airway inflammation is now proposed as a principal factor in airway responsiveness, therapeutic agents to prevent or reverse this abnormality are considered first-line therapy.

Tailoring General Therapy Guidelines to Individual Patient Needs

Asthma is a disease that varies among patients. The degree of an individual's asthma severity may change from one season or year to the next. Therefore, specific asthma therapy must be selected to fit the needs of individual patients. In addition, asthma therapy must be adaptable to change as the disease changes in the individual.

Because airway inflammation is now proposed as a principal factor in airway hyperresponsiveness, therapeutic agents to prevent or reverse this abnormality are considered first-line therapy.

The severity of asthma is often not appreciated by either patient or physician on routine evaluation. However, by determining the extent to which activity is limited, by evaluating nighttime symptoms, and by assessing pulmonary function (by both spirometry and peak flow determinations), the physician will be better able to begin *appropriate* therapy for a patient. It is also essential that therapeutic selections not have adverse effects that are perceived by the patient to be worse than the underlying disease.

The individual patient's asthma therapy will be dictated by the severity of disease, medication tolerance, and sensitivity to environmental allergens. All these factors need to be incorporated in the formulation of therapy.

Treating Asthma Triggers and Associated Conditions

It is essential to deal with common asthma triggers. Environmental control measures must be undertaken to avoid known allergens. Furthermore, it is essential that patients not smoke tobacco and that exposure to passive smoke be eliminated as much as possible (see Chapter 6, Managing Allergy in the Asthma Patient).

Inhaled beta$_2$-agonists or cromolyn sodium or both taken prior to an anticipated encounter with a known trigger can prevent or diminish an asthmatic response. This is well demonstrated in exercise-induced asthma (see Chapter 9, Exercise-Induced Asthma). The same principles can be applied to other situations, including exposure to antigen (e.g., animal dander), cold air, or other irritants. However, because beta$_2$-agonists block symptoms during exposure, their use prior to antigen exposure may lead the patient to remain longer in the contaminated environment. This may result in a greater likelihood of asthma symptoms occurring about 4-6 hours later. However, cromolyn sodium taken before antigen exposure blocks this late reaction to antigen.

There is increasing evidence that exacerbations of upper airways disease can provoke asthma. For younger children, viral upper respiratory syndromes are most commonly implicated and have no specific therapy. However, parents should be instructed that when children have viral infections, parents need to be vigilant about adhering to the regular asthma medication treatment plans, and they must be particularly alert for early signs of an acute asthma episode so that asthma medication may be started or increased immediately. Some children have an established pattern in

Figure 7-1
Goals of Asthma Therapy

- Maintain normal activity levels (including exercise).
- Maintain (near) "normal" pulmonary function rates.
- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion).
- Prevent recurrent exacerbations of asthma.
- Avoid adverse effects from asthma medications.

which asthma deteriorates rapidly every time they have a viral respiratory infection. For these selected patients, it may be appropriate to institute a short course of oral corticosteroid therapy at the earliest sign of viral respiratory infection rather than waiting for acute asthma symptoms to develop. Viral respiratory infections may also be a significant trigger for adults with asthma. Adults who have upper respiratory infections and start to have acute asthma symptoms may need to add or increase anti-inflammatory asthma medications in order to control the asthma symptoms.

Bacterial otitis and sinusitis may be associated factors for asthma for all age groups. Antibiotic therapy for 10 days to 3 weeks, depending on the chronicity of the patient's history of ear or sinus disease, can hasten control of asthma. It is not uncommon to see even aggressive asthma therapy fail because an upper respiratory infection has been overlooked. Antimicrobial therapy is necessary if a bacterial infection is present in the airways, but it remains an adjuvant to primary antiasthma therapy.

Influenza vaccinations and pneumococcal vaccine should be considered for patients with moderate or severe asthma in order to avoid aggravation of asthma.

Allergic and nonallergic rhinitis should be treated with antihistamines, cromolyn sodium nasal spray, or topical nasal corticosteroids.

Using Step-Care Pharmacologic Therapy

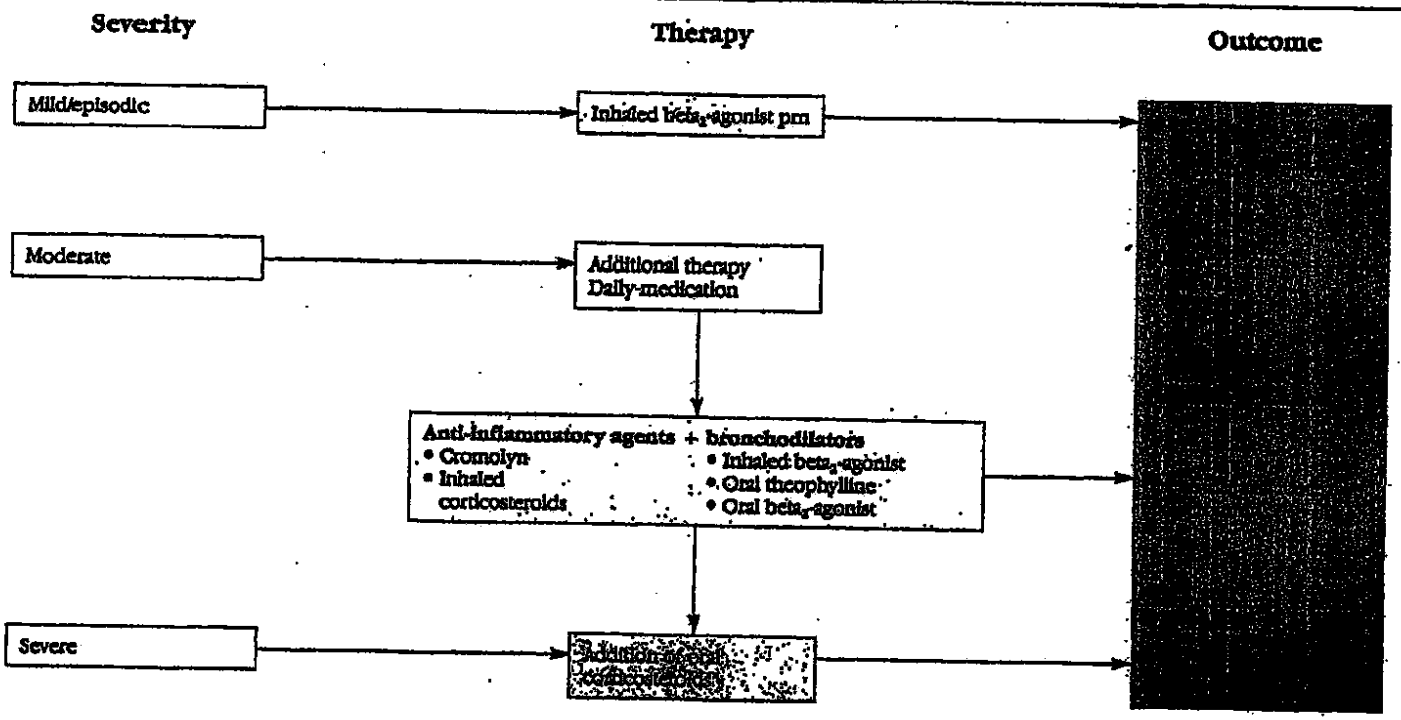
The approach to pharmacologic therapy is often described as "step-care," in which the number of medications and frequency of administration are increased as necessary. The possibility of toxicity is also increased with this approach. In general, the patient *must* have medication, an inhaled beta$_2$-agonist, available for acute relief of symptoms. Furthermore, if symptoms occur frequently (e.g., more than two times a week), preventive therapy is necessary in addition to rescue treatment. Rescue treatment itself has a step-care pattern, adding medications as necessary to control symptoms. However, this escalation is often temporary and depends on the severity and duration of the asthma exacerbation as well as the patient's response. Increasing use of rescue treatment by the patient is an indication to review the medication plan and possibly to increase preventive therapy. The flow chart on the following page (Chart 1) depicts the overview of asthma therapy.

Asthma can be classified into arbitrary groups based upon disease severity (see Figure 1-4 in Chapter 1, Definition and Diagnosis); therapeutic approaches within the classification are presented in the following protocols. The physician, however, must be aware that the severity of asthma is often underestimated; the precise intensity of airway disease often becomes apparent only upon close questioning and pulmonary function monitoring.

For patients who have established control of their asthma, regular follow-up visits (at approximately 1- to 3-month intervals) are still necessary to review the treatment plan, medication supplies, and the patient's management techniques (use of medicines, peak flow meters, etc.). Chapter 5, Patient Education, provides sample guidelines to give patients.

For many patients with moderate to severe asthma, control of asthma (reflected in normalization of pulmonary function and in activity levels without symptoms) can be maintained only with continuous preventive therapy. The aim of therapy is to use the optimum medication needed to maintain control with minimal risk for adverse effects. Reduction of therapy can be carefully considered if peak expiratory flow rate (PEFR) variability is less than 10 percent and there are no asthma symptoms for a reasonable period (2-3 days for the exacerbation in mild asthma, several weeks for moderate or severe asthma). Conversely, if PEFR variability is greater than 10-20 percent, the following variables must be reevaluated: the patient's technique in using medication, environmental aggravators and the patient's environmental control efforts, the possibility of concomitant upper respiratory disease, and, finally, the possibility that medications may need to be increased.

Management of Asthma
*Overview of Therapy**



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*All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.

Managing Special Problems

Special problems of asthma management include seasonal asthma and cough variant asthma.

Seasonal Asthma

Some patients experience asthma only in relationship to environmental allergens, i.e., pollens, molds, and house-dust mites. Basically, these individuals can be treated similarly to other patients, depending upon the severity of asthma symptoms. If the patient has seasonal symptoms on a predictable basis, prophylactic antiasthma therapy should be initiated prior to the anticipated onset of symptoms.

Cough Variant Asthma

Some patients, especially young children, will have cough as their principal symptom. Frequently, this occurs at night; consequently, examinations during the day are normal. If the patient is old enough to cooperate, a methacholine test may help detect these individuals when pulmonary functions are normal. In other patients, nocturnal administration of bronchodilators will be therapeutic and diagnostic.

Referring to a Specialist

It is recommended that an asthma specialist evaluate patients with moderate or severe asthma to conduct pulmonary function studies, to evaluate the role of allergy and irritants in the patient's asthma, and to evaluate the medication plan if the goals of therapy are not achieved.

Protocol for Management of Asthma in Adults

A treatment plan for adult asthma is based on general principles for managing asthma as well as considerations specific to the adult patient. This section focuses on these considerations. Flow diagrams (Charts 2, 3, and 4) accompany the discussion. Refer to Pharmacologic Therapy in Chapter 4 (Overview of Approaches to Asthma Therapy) for a review of the general properties of the pharmacologic agents recommended below.

Chronic Mild Asthma

The following discussion accompanies Chart 2.

Patients with mild or episodic asthma usually have no baseline abnormalities in pulmonary function, but demonstrate airway hyperresponsiveness clinically and mild airway obstruction episodically (fall less than 20 percent). For these patients, asthma symptoms often arise following exercise, exposure to irritants, allergic reactions, or respiratory infections. Treatment prior to anticipated exposure to exercise or antigen is often effective, as discussed earlier in this chapter.

During symptomatic periods, inhaled $beta_2$-agonists are usually sufficient to control asthma. If symptoms disappear and pulmonary function normalizes with inhaled $beta_2$-agonists, these agents can be used indefinitely on an as needed (prn) basis. However, use of inhaled $beta_2$-agonists more than three to four times per day or use of an inhaled $beta_2$-agonist on a daily basis usually indicates a need for additional therapy (see below: Moderate Asthma).

Oral theophylline does not usually give prompt bronchodilation; its use is recommended for continuous, not episodic, therapy.

Chronic Moderate Asthma

The following discussion accompanies Chart 3.

The next category of severity includes those patients who have symptoms that are not controlled or that are poorly regulated by episodic administration of a $beta_2$-agonist. Included in this category are patients who have frequent symptomatic exacerbations of asthma (more than twice a week). In these individuals, asthma symptoms are often most apparent at night, with activity, or in the presence of environmental triggers.

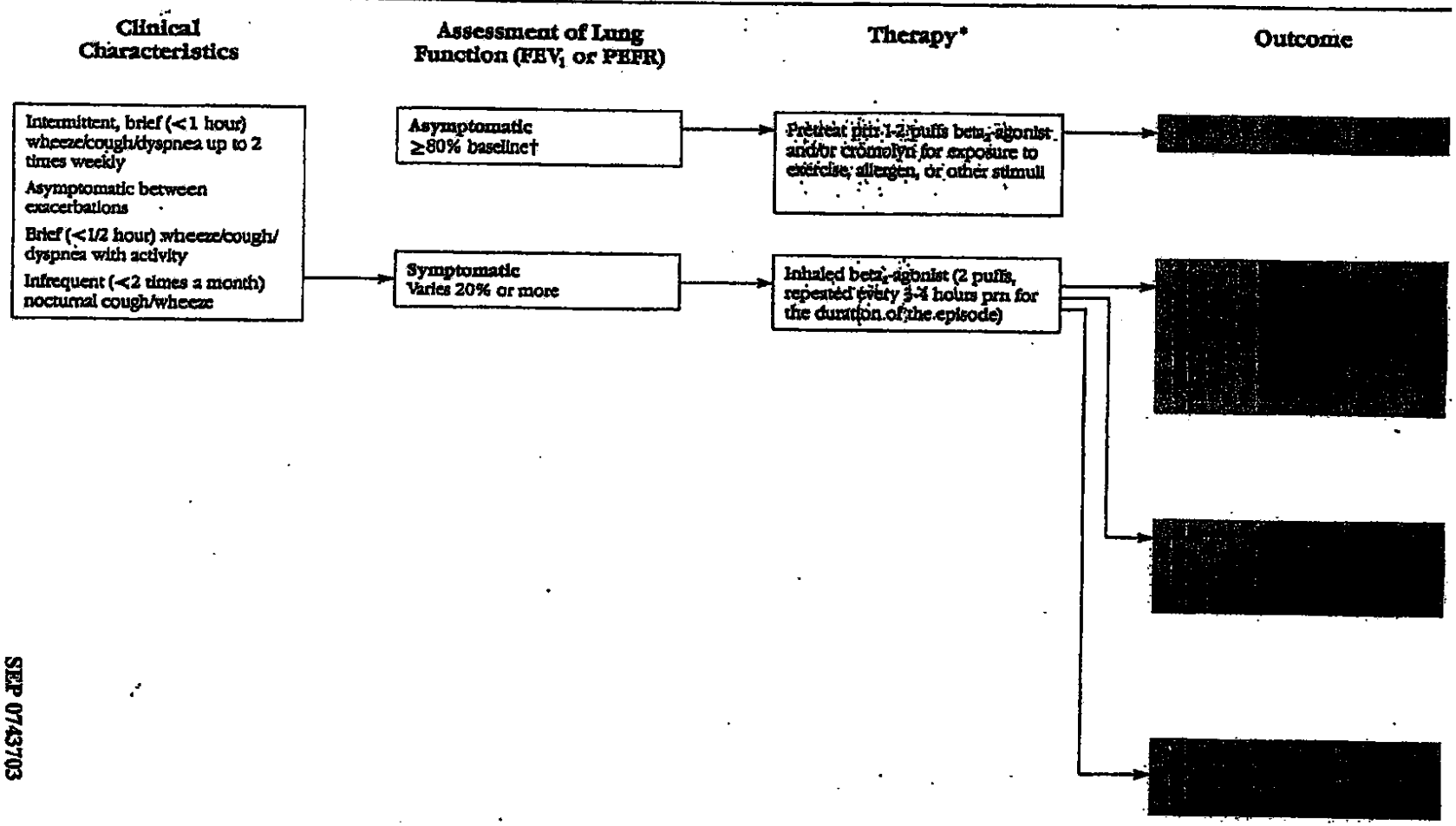
In treating moderate asthma, the physician has several choices of bronchodilators. Regular administration of inhaled $beta_2$-agonists is often effective. However, there is some evidence that prolonged administration of regularly scheduled inhaled $beta_2$-agonists may be associated with diminished control of asthma, as discussed earlier (in the discussion on bronchodilators in Chapter 4). If the patient exceeds three to four doses a day of a $beta_2$-agonist, additional therapy should be considered. Furthermore, currently available $beta_2$-agonists have limited duration of action (4-6 hours). Consequently, the patient is often left unprotected, especially at night. Sustained-release oral $beta_2$-agonist or sustained-release theophylline (sustaining bronchodilation for up to 12-24 hours) may be helpful in this situation. For the patient with primarily nocturnal symptoms, sustained-release theophylline or long-acting oral $beta_2$-agonist once a day in the evening may control symptoms and airway obstruction.

The physician must be aware that theophylline is not as potent a bronchodilator as $beta_2$-agonists and that many patients have an intolerance

art 2

Management of Asthma in Adults

Chronic Mild Asthma



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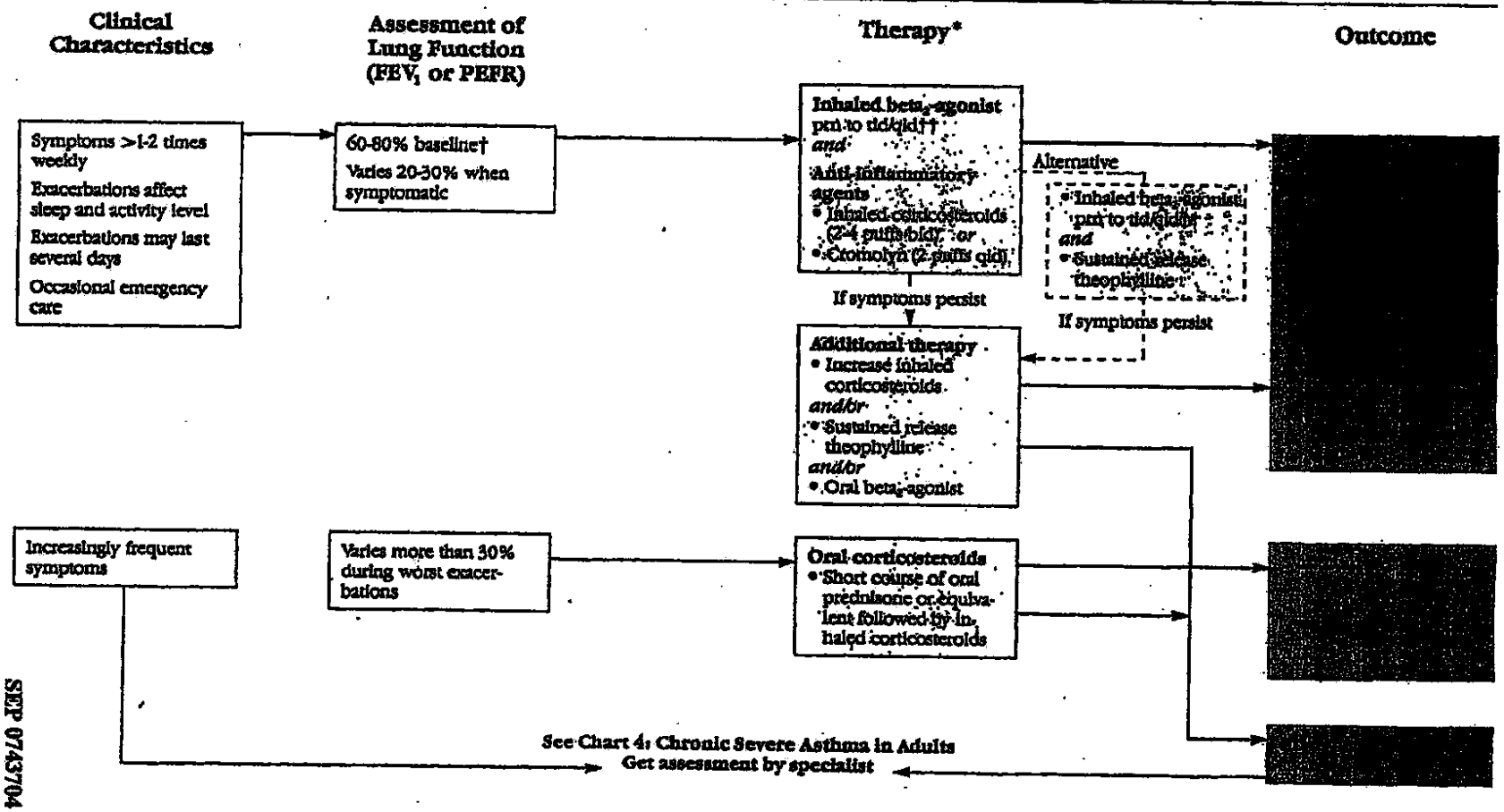
†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted of standardized norms or % patient's personal best.

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

art 3

Management of Asthma in Adults

Chronic Moderate Asthma



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†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best.

††If exceed 3-4 doses a day, consider additional therapy other than inhaled beta2-agonist.

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

of xanthine derivatives as indicated by gastrointestinal distress, nervousness, insomnia, or headaches. Although theophylline's therapeutic efficacy usually correlates with serum theophylline concentration within the range 5-15 μg/mL, patients (especially those with milder disease) may occasionally benefit from doses producing serum levels of 5-10 μg/mL (see Chapter 4).

If theophylline is the primary bronchodilator for a given patient, beta$_2$-agonist therapy can be administered episodically.

Anticholinergic use in asthma requires further evaluation. Although some asthma patients respond to anticholinergics, this response is less predictable than with beta$_2$-agonists. Furthermore, anticholinergics have a slower onset of action with peak bronchodilation obtained in 30-90 minutes. Patients who have adverse reaction to beta-blocking agents (e.g., propranolol or other beta blockers) may respond to anticholinergic medication for the acute exacerbation.

Increasing evidence suggests that airway inflammation is present in virtually *all* patients with asthma and that anti-inflammatory therapy should be considered for patients with moderate asthma. Currently, the physician has two choices, cromolyn or inhaled corticosteroids. Experience in Europe and Australia indicates that high-dose, inhaled corticosteroids (e.g., 1,600 to 2,600 μg/day beclomethasone) suppress airway hyperresponsiveness; there is also evidence that similar effects are achieved with smaller doses (400 to 800 μg) in milder cases. Confirmation of these observations is necessary. Nonetheless, the aggressive use of these agents (400 to 800 μg per day) may provide improved asthma care with minimal side effects. (Concentrations per inhalation vary among the corticosteroid formulations beclomethasone, triamcinolone, and flunisolide—see Figure 7-2. The doses cited here are illustrative and refer to beclomethasone. In the absence of complete data, the same dosage guidelines may be applied to the other formulations. However, the relative anti-inflammatory, steroid-suppressive effects of these three distinct formulations have not been established.)

Cromolyn sodium also has been advocated for anti-inflammatory activity. Cromolyn sodium is virtually devoid of any side effects, but its effectiveness in asthma is less predictable than that of inhaled corticosteroids in all patients treated.

Patients who use sustained-release theophylline (or oral beta$_2$-agonist) medication to control nocturnal symptoms and who also take anti-inflammatory medication may be able to discontinue bronchodilator usage after 4-6 weeks of anti-inflammatory therapy.

Often, asthma is not controllable by *any* combination of bronchodilators (beta-adrenergic agonists and/or theophylline), cromolyn sodium, or inhaled corticosteroids. When asthma is exacerbated to this degree (but not to a degree requiring emergency department care), a short burst of systemic corticosteroid therapy is indicated.

Deterioration of asthma is characterized by gradual reductions in PEFR (approximately 20 percent) that fail to have a sustained response to inhaled bronchodilators, greater intolerance of activities or exercise, and the development of nocturnal symptoms. Increasing the dose of inhaled corticosteroids (e.g., from 400 to 800 μg per day) may control symptoms. However, a burst, or short tapering course, of oral corticosteroids is often necessary. For example, 40 mg prednisone/day (single or divided dosing) for 1 week followed by 7-14 days of tapering doses may be effective. At the completion of this therapeutic deescalation, oral corticosteroids can be stopped. If asthma symptoms do not occur and pulmonary functions remain normal, no additional therapy is necessary.

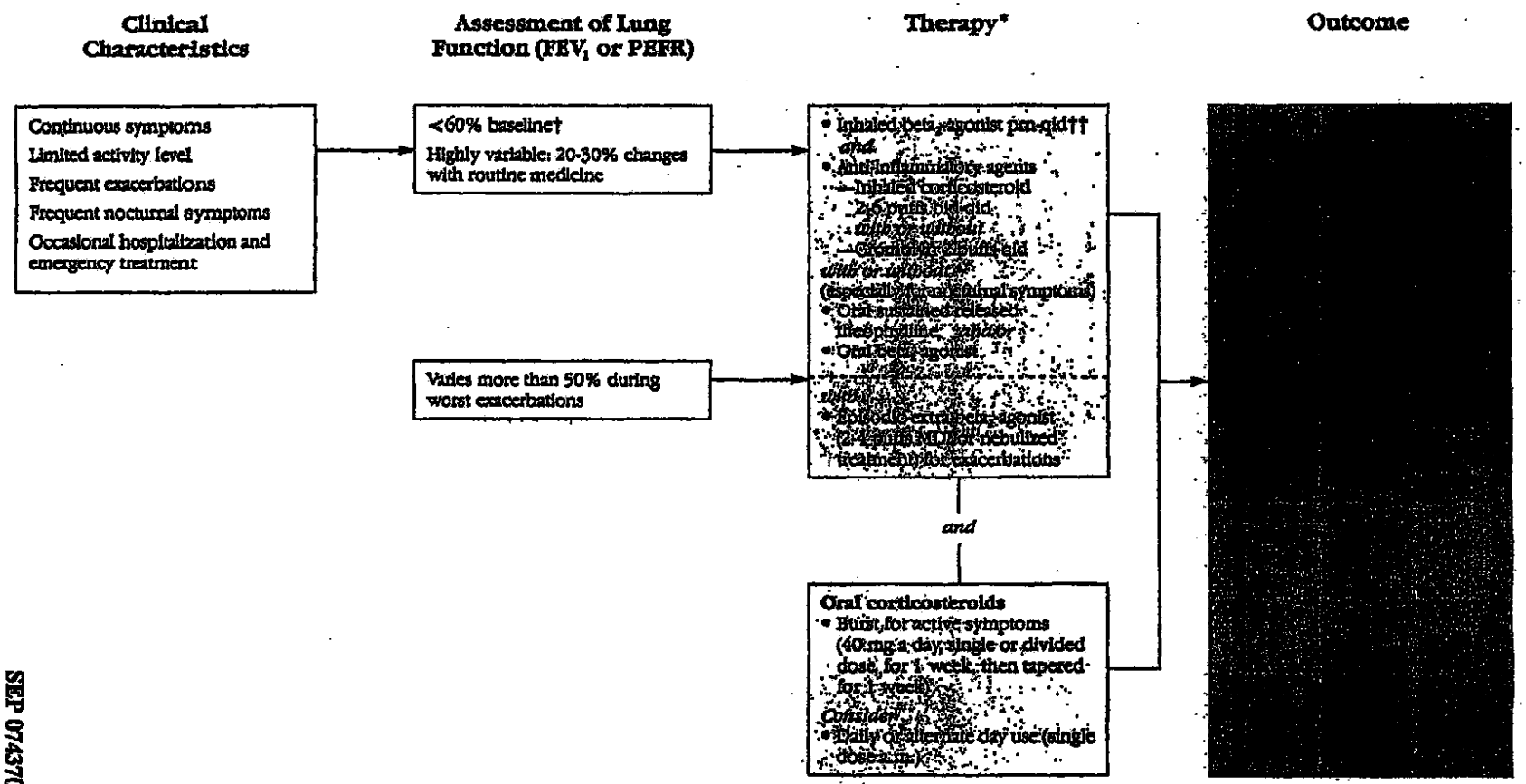
The burst of prednisone often does not control symptoms, or the control is short-lived (less than 10-14 days). Furthermore, patients who require frequent bursts of prednisone have severe asthma and obviously need additional therapy. If the patient with unstable asthma is not already taking inhaled corticosteroids, therapy using these agents should be started. Inhaled beclomethasone (400 to 800 μg per day), triamcinolone, or flunisolide can be very effective in this situation. Some patients may benefit from higher doses (e.g., 1,000 μg beclomethasone per day). Immediate benefit will not be evident because suppression of symptoms and PEFR improvement are often not maximal until 2-4 weeks of treatment.

In most patients with moderate asthma, symptoms are only marginally controlled by bronchodilators. Although these patients do not have acute exacerbations of asthma and can regulate symptoms by modulation in lifestyles, their pulmonary functions (FEV_1 or PEFR in the 60-80 percent predicted range) indicate compromises in airway function. These patients have very "fragile" control of asthma, and the introduction of inhaled steroids or cromolyn sodium is appropriate and often of great benefit. Furthermore, many specialists in asthma treatment think that *all* patients with asthma (other than mild, episodic asthma) should receive inhaled anti-inflammatory medication to diminish airway inflammation and, hence, airway hyperresponsiveness. Current studies with cromolyn sodium or inhaled corticosteroids suggest that this should be a highly beneficial approach.

Chart 4

Management of Asthma in Adults

Chronic Severe Asthma



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Note: Individuals with severe asthma should be evaluated by an asthma specialist.

†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted of standardized norms or % patient's personal best.

††If exceed 3-4 doses a day, consider additional therapy other than inhaled beta2-agonist.

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Chronic Severe Asthma

The following discussion accompanies Chart 4.

Patients who are not controlled on maximal doses of bronchodilators and cromolyn or aerosolized corticosteroids pose a major problem. These patients are often at risk for severe exacerbations. Some need systemic corticosteroids on a routine basis, and in this case, the physician is tied to the use of long-term oral corticosteroids. The lowest possible dose must be sought (alternate-day or single daily dose) and should be administered under the supervision of an asthma specialist. Patients under this form of therapy must be monitored closely for corticosteroid side effects (hypertension, diabetes, osteoporosis, cataracts, mental changes) (see Chapter 4), and attempts to reduce prednisone should be made continually with persistent administration of maximal doses of inhaled corticosteroids (e.g., 800 μg or more per day of beclomethasone). Use of a spacer with the inhaled corticosteroids may help prevent oral candidiasis.

For patients with more severe disease, the administration of experimental anti-inflammatory drugs such as methotrexate and gold is being evaluated. Preliminary data indicate that such an approach may be beneficial in highly selected patients. However, the role these forms of therapy have in the treatment of asthma is unclear, and they should be used only under the supervision of an asthma specialist experienced in their use (see Chapter 4).

Protocol for Management of Asthma in Children

This section and the accompanying flow diagrams (Charts 5, 6, and 7) discuss the application of general principles of asthma care to the management of childhood asthma. Figure 7-2 at the end of the section summarizes information on dosages for treatment of childhood asthma.

The recommendations relate asthma severity to objective peak expiratory flow rate (PEFR) determinations. For children under 5 years of age, the PEFR is either not attainable or too dependent on fluctuating levels of attention and effort to be reliable. For younger children, the history and physical examination, while imperfect, are essential elements for decision making.

Chronic Mild Asthma

The following discussions accompany Chart 5.

Mild asthma is characterized by episodes of wheezing that cause PEFR or FEV_1 to decrease by 20 percent or less and by asymptomatic periods between exacerbations. Symptomatic exacerbations may occur infrequently or up to twice a week and are generally of brief duration and mild severity.

Although children ages 3-5 years are sometimes able to perform PEFR determinations reliably, interpretations obtained in children under 5 years of age often will not be valuable. Symptom assessment, while imprecise, must be done carefully. Cough, wheeze, disruption of activity, and nocturnal awakening should be assessed. With mild asthma, cough and wheeze are intermittent. Disruption of activity and nocturnal awakening are uncommon and suggest the more severe obstruction of moderate asthma.

The medication of choice for mild, intermittent asthma is beta$_2$-agonist on an as needed (prn) basis. Choices of administration of the therapy for mild asthma in children depend largely on the patient's age. Beta$_2$-agonist can be inhaled. When administered this way, onset of action is quick, and the incidence of adverse effects is low. Patients over 5 are able to use metered-dose inhalers (MDI); those under 5 usually cannot. For some children ages 3-5 years (and older children who have difficulty with the technique), a spacer device used with an MDI will eliminate the problem of synchronizing actuation and inhalation. These devices provide a holding chamber for medication and allow the child to inhale when he or she is ready. This can lower the age when MDIs become practical for children. A device that combines a face mask with a spacer may also decrease the age at which MDIs can be used, although data evaluating this device are limited. Dry powder inhalers, which use an inhalation technique that requires less synchronization than MDIs, may also be considered.

Nevertheless, for most children under 5, one must choose between oral and nebulized medication. Because nebulized beta$_2$-agonist medication is more effective and has fewer adverse effects (such as tremor and irritability), it is preferable for the child who has infrequent exacerbations but is nevertheless significantly compromised by them. The disadvantages of nebulizer therapy are the initial expense of the device and the difficulty in transporting it (e.g., to day care). Therefore, children may take a combination of oral medications at certain times (away from home) and nebulized medication at other times (at home).

Chart 5

Management of Asthma in Children

Chronic Mild Asthma

Clinical Characteristics	Assessment of Lung Function (FEV_1 or PEFR)	Therapy*	Outcome
Intermittent, brief (<1 hour) wheeze/cough/dyspnea/tightness up to 2 times weekly Asymptomatic between exacerbations Brief (<1/2 hour) wheeze/cough/dyspnea with activity Infrequent (<2 times a month) nocturnal cough, wheeze	Asymptomatic ≥80% baseline†	Pretreat prn 1-2 puffs beta$_2$-agonist and/or cromolyn for exposure to exercise, allergen, or other stimuli	[redacted]
	Symptomatic Varies more than 20%	Beta$_2$-agonist prn • <5 years nebulized or oral; see dose chart • ≥5 years inhaled 2 puffs or 1 inhaled dry powder capsule every 4-6 hours prn for the duration of the episode	[redacted]
			[redacted]
			[redacted]

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†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted of standardized norms or % patient's personal best.

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Therapy should be initiated when early symptoms occur or, if PEFR is monitored, when PEFR declines more than 10-20 percent. Therapy should be continued every 4-6 hours until PEFR stabilizes or there is sustained improvement of symptoms. For children under 5 years of age, symptoms of cough and dyspnea replace peak expiratory flow rate as the focus for therapeutic decisions. If the patient over 5 years of age with mild asthma experiences increasingly frequent symptoms, it is appropriate to initiate a period of PEFR monitoring at home in order to evaluate the severity of asthma (see Chapter 2, Objective Measures of Lung Function). Patients are considered to have moderate asthma if the PEFR drops 10-20 percent more often than twice weekly (aside from exacerbations of exercise-induced asthma, described in Chapter 9). Chronic prophylactic therapy is then recommended.

Chronic Moderate Asthma

The following discussion accompanies Chart 6.

Patients who have more than two acute asthma exacerbations per week, with PEFR or FEV_1 decreasing 20 percent or more (from predicted or personal best), are considered to have moderate asthma. These patients should use $beta_2$-agonist on an as needed (prn) to a two-to four-times-a-day (bid-qid) basis along with other regular therapy. Children over 5 years of age should have a $beta_2$-agonist bronchodilator in the form of an MDI or dry powder inhaler, whereas children under 5 years will usually require a home nebulizer. Occasionally an oral $beta_2$-agonist may be useful.

To avoid frequent fluctuations in PEFR and asthma symptoms as well as overuse of $beta_2$-agonist, additional therapy is needed. There are three choices: cromolyn sodium, inhaled corticosteroid, or sustained-release theophylline.

Cromolyn sodium is not systemically absorbed and thus is free of the systemic side effects sometimes encountered with theophylline. In addition, cromolyn sodium appears to provide anti-inflammatory activity. Children over 5 years of age can use cromolyn sodium by MDI; children under 5 years must use a nebulizer unless they successfully master an MDI with a spacer device. Cromolyn sodium therapy could be initiated with a three-to four-times-a-day (tid-qid) regimen. However, many patients can be successfully managed on a twice-a-day regimen.

Inhaled corticosteroid provides excellent anti-inflammatory therapy and is an acceptable primary therapy for moderate asthma, although a trial of cromolyn sodium should usually precede its use because of the extensive clinical experience with and study of cromolyn sodium. The use of inhaled corticosteroid is recommended for patients over 5 years of age who are taking cromolyn sodium but who continue to need a $beta_2$-agonist more than three to four times a day or who continue to have nocturnal symptoms. After the patient stabilizes on the inhaled corticosteroid, usually after a period of 2-4 weeks, the cromolyn sodium may be discontinued.

Sustained-release theophylline is an alternative primary asthma therapy, although it is a subject of current debate whether or not theophylline provides anti-inflammatory activity. Sustained-release theophylline preparations are given in oral doses intended to achieve a serum concentration of 5-15 μg/mL. There appears to be a linear relation between log serum concentration and bronchodilator effect within this 5-15 μg/mL therapeutic range. Therefore, a patient's theophylline dose should be increased if symptoms persist and the patient is at the lower end of the serum concentration range. Although theophylline offers the ease of administration of an oral drug, it may cause side effects such as irritability and gastrointestinal upset even at doses giving appropriate therapeutic concentrations. Serum concentration must be monitored periodically to be certain that the patient is within the proper therapeutic but not toxic range. Sustained-release theophylline may be particularly helpful to patients who have primarily nocturnal symptoms because it is a long-acting bronchodilator. For these patients, a single evening dose of theophylline may control symptoms. However, persistent nocturnal symptoms may be an indication that the patient's asthma requires more aggressive therapy, including anti-inflammatory medications.

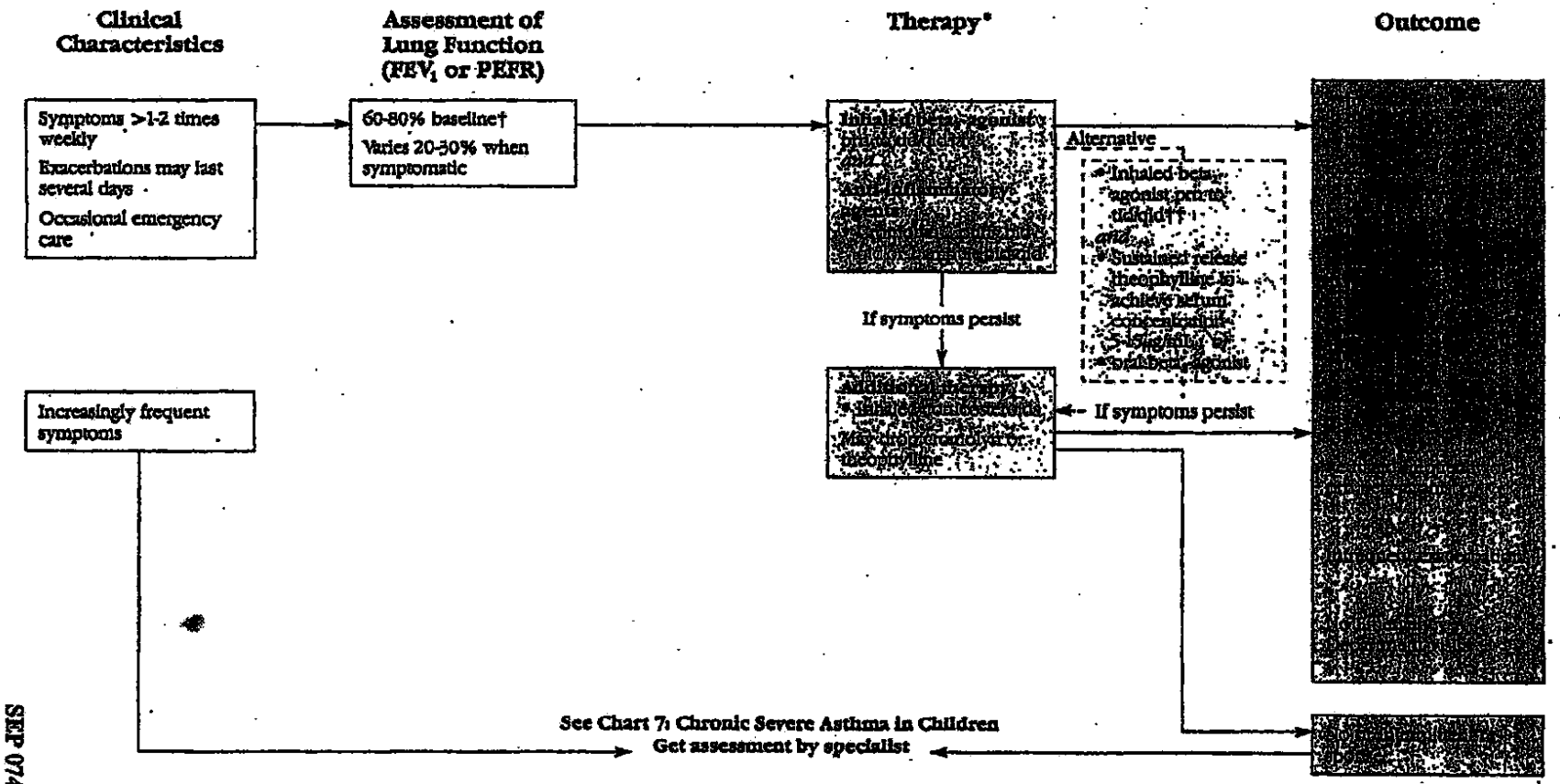
With regular use of cromolyn sodium, inhaled corticosteroid, or theophylline, the use of $beta_2$-agonist should be reduced to an infrequent prn (as needed only) therapy. Thus, $beta_2$-agonist serves as symptom reliever or rescue therapy, whereas cromolyn sodium, inhaled corticosteroid, or theophylline therapies serve as preventive or maintenance therapy.

An asthma specialist should be consulted if PEFR fluctuations (or asthma symptoms in young children) continue, if the child's personal best PEFR does not reach 90 percent of predicted or personal best, if decisions about therapy are unclear, or if the role of allergy needs to be investigated.

Chart 6

Management of Asthma in Children

Chronic Moderate Asthma



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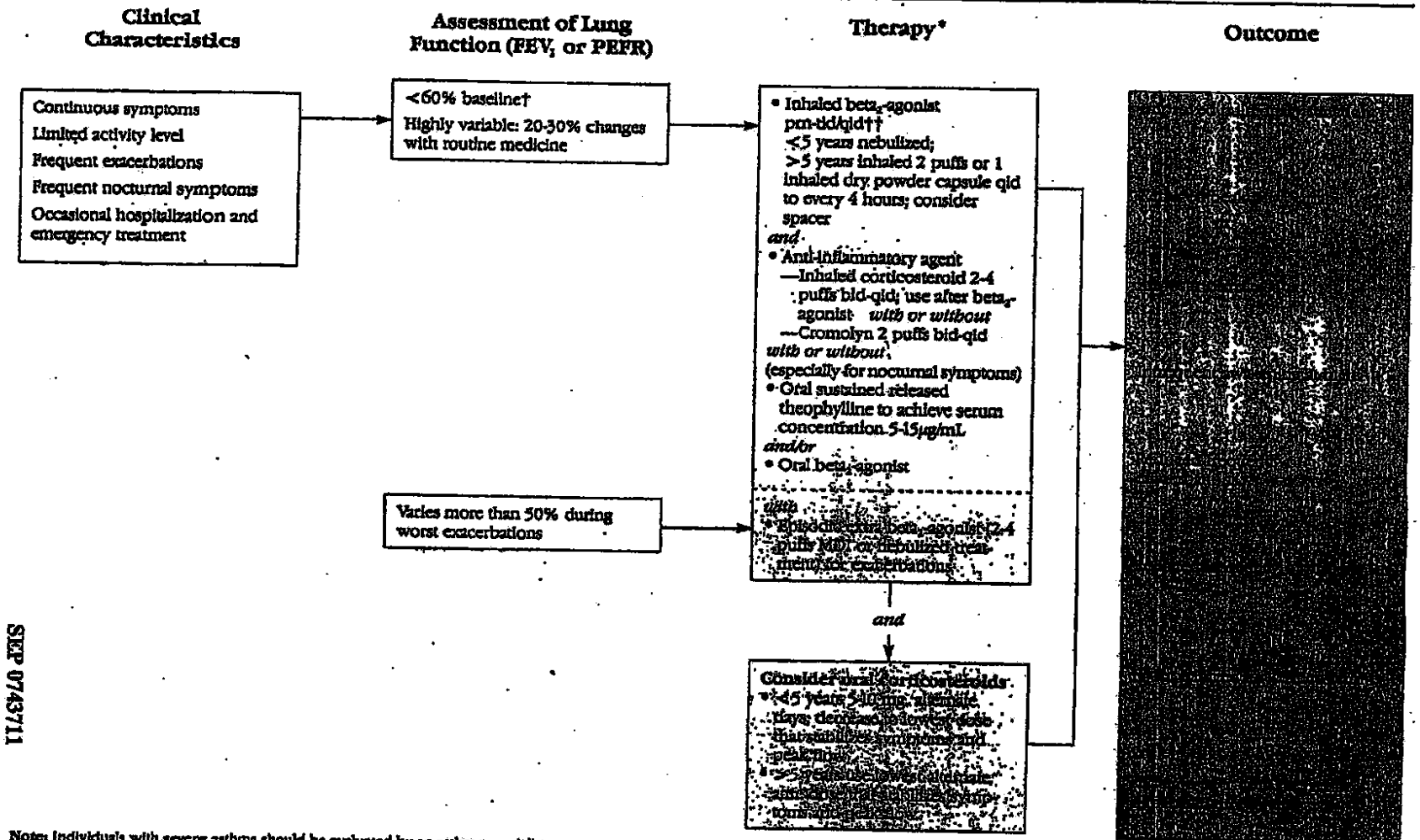
†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best.

††If exceed 3-4 doses a day, consider additional therapy other than inhaled $beta_2$-agonist.

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Management of Asthma in Children

Chronic Severe Asthma



Note: Individuals with severe asthma should be evaluated by an asthma specialist.

†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted of standardized norms or % patient's personal best.

††If exceed 3-4 doses a day, consider additional therapy other than inhaled beta2-agonist.

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Chronic Severe Asthma

The following discussion accompanies Chart 7.

Patients with severe asthma should be evaluated by an asthma specialist.

Patients whose symptoms continue despite the foregoing therapy usually have PEFR or FEV_1 fluctuations of 20-30 percent between the premedication and postmedication measures. They also may have precipitous drops in PEFR or FEV_1 during their worst exacerbations (see Chapter 8, Management of Acute Exacerbations of Asthma). For daily therapy, these patients require bronchodilators including theophylline and a $beta_2$-agonist prn (or as needed) to tid-qid in addition to corticosteroids.

Patients over 5 years of age should use an inhaled corticosteroid because of its excellent anti-inflammatory capability. Younger children should use oral steroids because they are generally unable to use inhalers effectively. Inhaled corticosteroids are preferred for children over 5 years old because of the minimal adverse effects of these medications; however, older children may use oral corticosteroids if questions of cost or compliance arise. The oral form is less expensive and easier to use. Oral corticosteroids should be given as a single alternate-day, early-morning dose to minimize steroid adverse effects.

With both inhaled $beta_2$-agonists and inhaled steroid MDIs, efficacy is enhanced and adverse effects are minimized by using a spacer device. These slow particle velocity and allow evaporation, resulting in smaller particle size. Both factors promote improved lower airway deposition of the drug. Spacers also decrease oral candidiasis and the incidence of dysphonia and hoarseness, which are sometimes seen with inhaled steroid use. It is best to avoid mixing different medications in the spacer.

Figure 7-2 summarizes information on dosages for treatment of childhood asthma.

Figure 7-2

Dosages for Therapy in Childhood Asthma

Beta$_2$-Agonists

Inhaled

Examples: Albuterol, metaproterenol, bitolterol, terbutaline, pirbuterol

Mode of administration	
—Metered-dose inhaler	2 puffs q 4-6 hours
—Dry powder inhaler	1 capsule q 4-6 hours
—Nebulizer solution*	Albuterol 5 mg/ml; 0.1-0.15 mg/kg in 2 cc of saline q 4-6 hours, maximum 5.0 mg Metaproterenol 50 mg/ml; 0.25-0.50 mg/kg in 2 cc of saline q 4-6 hours, maximum 15.0 mg

Oral

Liquids	Albuterol	0.1-0.15 mg/kg q 4-6 hours
	Metaproterenol	0.3-0.5 mg/kg q 4-6 hours
Tablets	Albuterol	2 or 4 mg tablet, q 4-6 hours 4 mg sustained-release tablet q 12 hours
	Metaproterenol	10 or 20 mg tablet q 4-6 hours
	Terbutaline	2.5 or 5.0 mg tablet q 4-6 hours

Cromolyn Sodium

MDI	1 mg/puff; 2 puffs bid-qid
Dry powder inhaler	20 mg/capsule; 1 capsule bid-qid
Nebulizer solution	20 mg/2 mL ampule; 1 ampule bid-qid

Theophylline

Liquid
Tablets, capsules
Sustained-release tablets, capsules

Dosage to achieve serum concentration of 5-15 μg/mL

Corticosteroids

*Inhaled***

Beclomethasone	42 μg/puff 2-4 puffs bid-qid
Triamcinolone	100 μg/puff 2-4 puffs bid-qid
Flunisolide	250 μg/puff 2-4 puffs bid

*Oral****

Liquids	Prednisone	5 mg/5cc
	Prednisolone	5 mg/5cc 15 mg/5cc
Tablets	Prednisone	1, 2.5, 5, 10, 20, 25, 50 mg
	Prednisolone	5 mg
	Methylprednisolone	2, 4, 8, 16, 24, 32 mg

**Premixed solutions are available. It is suggested that the perinj dosage recommendations be followed.*

***Consider use of spacer devices to minimize local adverse effects.*

****For acute exacerbations, doses of 1-2 mg/kg in single or divided doses are used initially and are then modified. Reassess in 3 days, as only a short burst may be needed. There is no need to taper a short (3- to 5-day) course of therapy. If therapy extends beyond this period, it may be appropriate to taper the dosage.*

For chronic dosage, the lowest possible alternate-day a.m. dosage should be established.

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8
Management of Exacerbations of Asthma

Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. Respiratory distress is also common. Exacerbations are characterized by decreases in expiratory airflow that can be documented and quantified by measurement of lung function (peak expiratory flow rate—PEFR—measurement or spirometry).

This chapter presents recommendations for managing acute exacerbations in home, physician's office, emergency department, and hospital settings. The first section provides an overview of treatment principles for managing exacerbations of asthma. Specific guidelines for the assessment and treatment of acute exacerbations in adults follow in the next section; guidelines for the assessment and treatment of acute exacerbations in children comprise the third section. The flow charts are provided as general guidelines considered applicable to most asthma patients; however, recommendations to a particular patient may need to be individualized.

Overview

The best strategy for management of asthma exacerbations is early treatment to prevent deterioration and abort the exacerbation. Important components of this prevention are:

- **Early recognition** of worsening lung function.
- **Prompt communication** between patient and health care provider regarding deterioration and treatment.
- **Appropriate intensification** of antiasthma medications. In many episodes, a short course of systemic corticosteroids can reverse an otherwise refractory asthma exacerbation and preclude the need for emergency care and possible hospitalization.
- **Removal of the allergen or irritant** if one or the other triggered the exacerbation. Treatment is less effective if there is continued exposure.

Patients should be taught to recognize early indicators of asthma exacerbations, and plans for co-management of the exacerbations with the clinician should be developed in advance. These patient skills are important components of patient education (see Chapter 5, Patient Education).

Failure to improve rapidly with treatment at home should lead to medical contact. Serious exacerbations require close observation, treatment with frequently inhaled beta$_2$-agonists and the early introduction of systemic corticosteroids, and repetitive measurements of lung function.

Some patients are at risk for exacerbations of asthma of such severity as to be potentially life threatening (see Chapter 3, Asthma Mortality). These patients require particularly intensive education, close monitoring, and prompt care. They should be counseled to seek medical care rather than increase bronchodilator therapy beyond recommended doses. They should also be instructed about the availability and appropriate use of ambulance services. This category of high risk for asthma-related death includes patients who have a history of:

- Prior intubation for asthma.
- Two or more hospitalizations for asthma in the past year.
- Three or more emergency care visits for asthma in the past year.
- Hospitalization or emergency care visit within the past month.
- Current use of systemic corticosteroids or recent withdrawal from systemic corticosteroids.
- Past history of syncope/hypoxic seizure due to asthma.
- Prior admission for asthma to hospital-based intensive care unit (ICU).
- Serious psychiatric disease or psychosocial problems.

Initial treatment of an asthma exacerbation can begin at home. Failure to improve rapidly at home should lead to medical contact. Serious exacerbations require close observation, frequent treatment, and repetitive measurements of lung function. Treatment should be given in a setting equipped to provide this intensity of care by clinicians qualified to manage patients with respiratory distress and to recognize impending (or actual) respiratory failure.

It may be appropriate to give initial treatment in a physician's office and, if the office is adequately equipped and staffed, to continue treatment there, especially if alternative facilities are not readily accessible. However, in most instances, and certainly in patients with respiratory distress, care should promptly be transferred to hospital-based emergency services.

The principles of care of acute asthma exacerbations can be summarized briefly:

- The principal goal of treatment is the rapid reversal of airflow obstruction, with accompanying relief of respiratory distress.
- Rapid reversal of airflow obstruction can be achieved by repetitive administration of inhaled beta$_2$-agonists.

■ Early addition of systemic corticosteroids speeds the rate of improvement among patients who fail to respond or respond incompletely to inhaled beta$_2$-agonists.

■ If present, hypoxemia needs to be corrected with administration of supplemental oxygen; in rare instances, severe hypoventilation requires mechanically assisted ventilation.

■ Close monitoring of the patient's condition and response to treatment, including serial measurements of lung function, is an essential part of care. The ranges for PEFR and FEV$_1$ presented in the protocols are offered as general guidelines, not precise markers, for treatment. It is not recommended to make decisions about therapy for acute exacerbations based solely on lung function measurement. Rather, PEFR and FEV$_1$ measures are meant to aid in a monitoring and decision making process that takes a number of factors into account, including the patient's clinical status.

Protocol for Management of Acute Exacerbations of Asthma in Adults

Home Management of the Exacerbation of Asthma

The discussion in this section accompanies Chart 8.

General Principles

The primary goal of home management of acute exacerbations of asthma is to avoid delays in initiating anti-asthma therapy by having the patient begin treatment at home. A secondary goal is for patients skilled in self-management to acquire a sense of control over their lives and their illness. It is equally important that the patient not delay seeking professional medical help if the asthma exacerbation is severe or if the response to therapy is not prompt and sustained.

The goal of self-management is NOT to shift care of the acutely ill asthma patient from a medical facility to the home.

It is recognized that, for any particular patient, the optimal management strategy may evolve out of months or years of patient and physician experience with what works and what does not in treating exacerbations of acute deterioration. Development of individualized crisis management plans tailored to the unique needs of specific patients is encouraged. The flow charts are provided as general guidelines considered applicable to most asthma patients; however, recommendations to a particular patient may need to be individualized.

Each patient should have available and be familiar with a written asthma action plan to be followed in the event of an exacerbation of asthma (see samples in Chapter 5, Patient Education). This plan should emphasize patient recognition of the early warning signs of an asthma exacerbation, including falls in PEFR measurements, the need to begin treatment promptly when those signs appear, and the need to remove an allergen or irritant if it triggered the exacerbation. Early treatment is the most effective. Patients with identified risk factors for asthma death (see the list in the Overview of this chapter and Chapter 3, Asthma Mortality) require specially tailored action plans and close monitoring.

Home PEFR determinations are an integral part of self-management strategies. They help the patient and clinician:

■ Assess the severity of the exacerbation. (Figure 5-4 identifies indices of a severe exacerbation.)

■ Assess the response to treatments taken.

■ Review important information at the time of telephone contact.

The following home management techniques are NOT recommended:

■ Drinking large volumes of liquids or breathing warm, moist air (e.g., the mist from a hot shower).

■ Rebreathing into a bag held tightly at the nose and mouth.

■ Taking over-the-counter antihistamines and cold remedies.

Pursed-lips or diaphragmatic breathing and other forms of controlled breathing may help to maintain calm during a period of respiratory distress. However, they do not bring about any improvement in lung function.

If there is no improvement after 1 hour or if there is deterioration, self-management should not be continued. If sustained improvement is not achieved, medical help should always be sought.

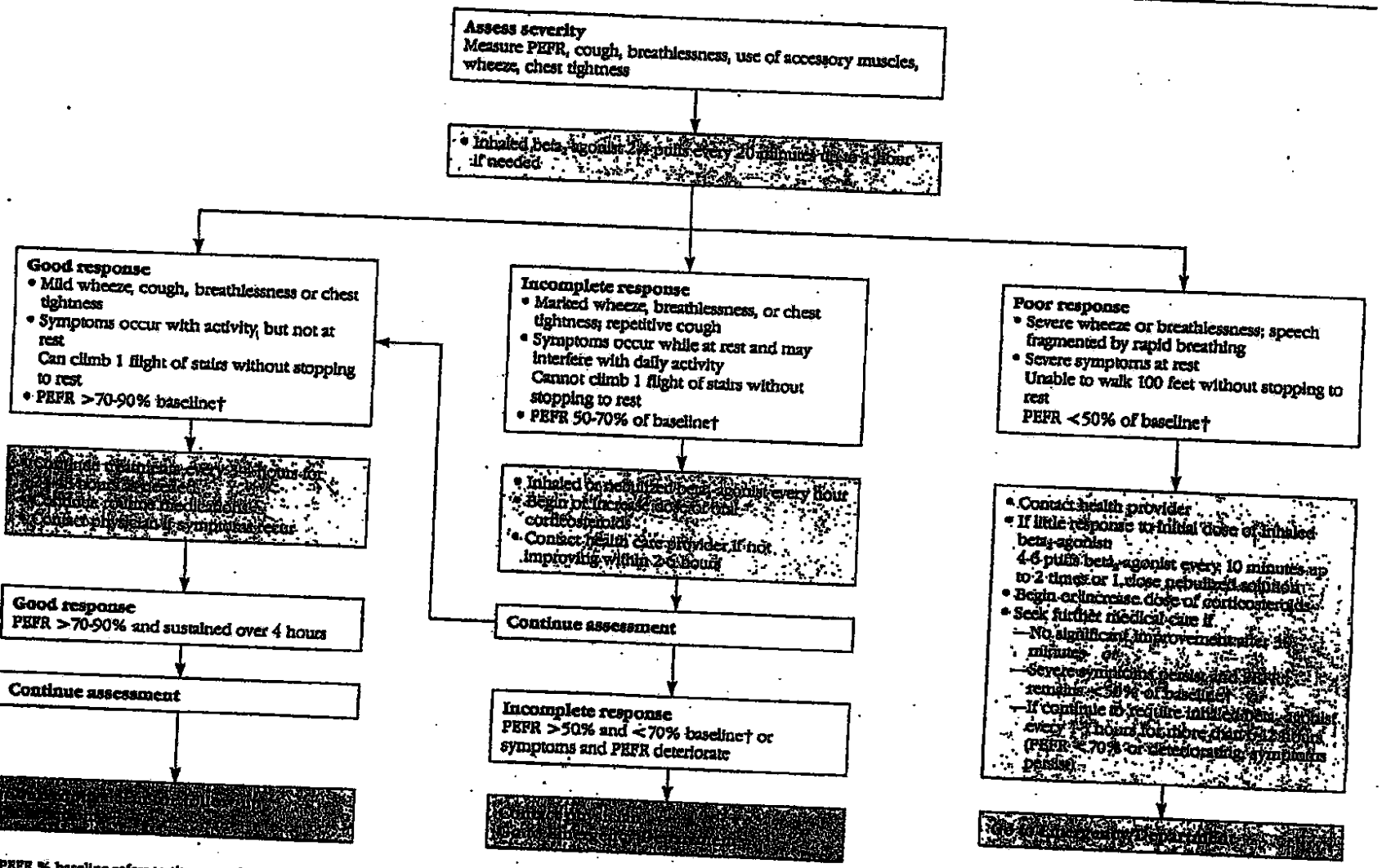
Recovery from an acute exacerbation is often gradual. Medications for acute therapy may need to be continued for several days to sustain improvement in PEFR and relief of symptoms.

Initial Treatment in the Physician's Office

Therapies that are often available in the physician's office and that may provide temporary relief or amelioration of respiratory distress are summarized for adults in Charts 8 and 9. (Charts 11 and 12 summarize this information for children.) The improvement afforded by these treatments is temporary, and their administration does not constitute a complete course of therapy for most acutely severe exacerbations of asthma.

Acute Exacerbations of Asthma in Adults

Home Management



†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best.

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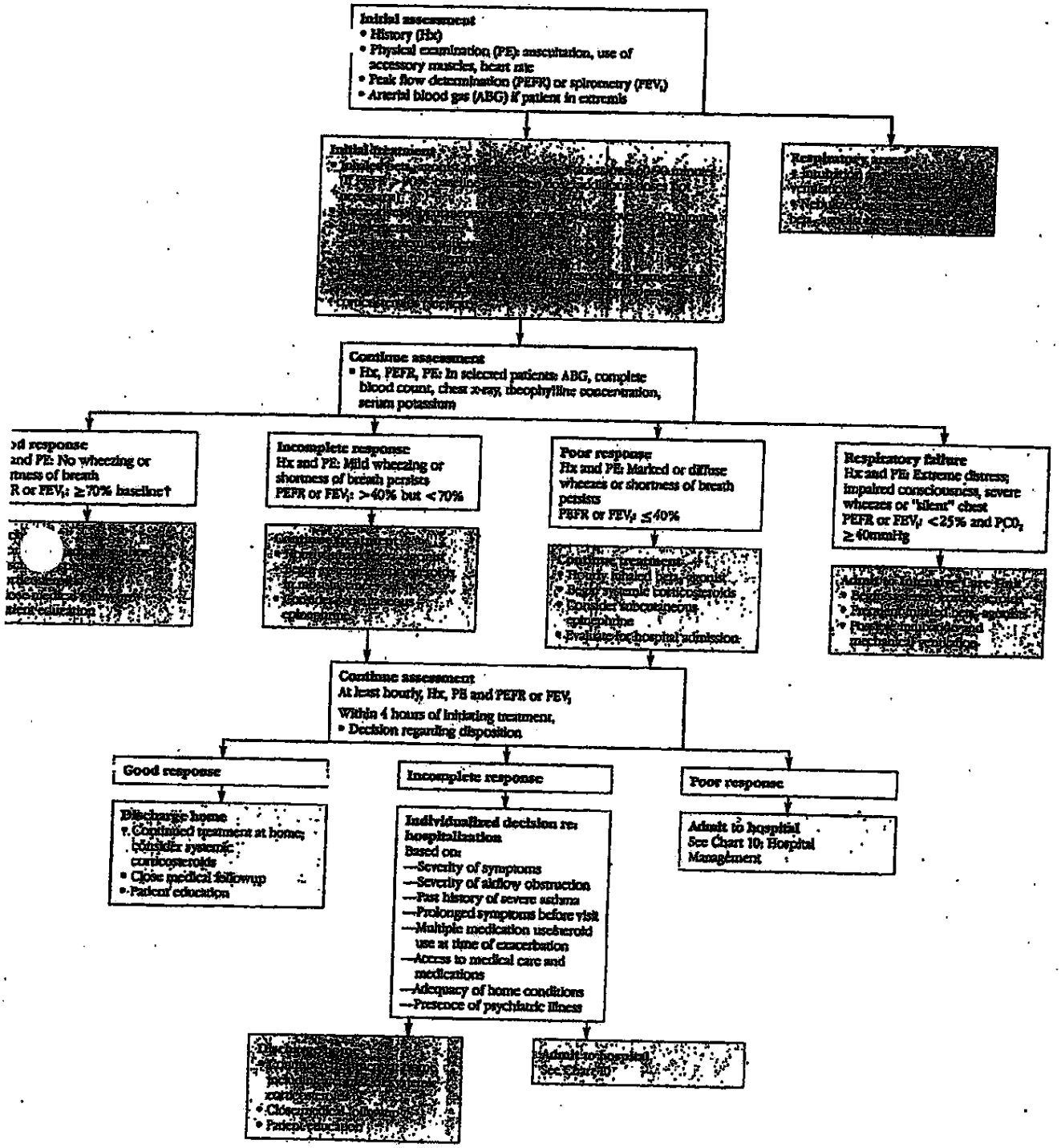
Chart 9

Acute Exacerbations of Asthma in Adults*

Emergency Department Management



rapid Ion available in a physician's office. However, most acutely severe exacerbations of asthma require a complete course of therapy in an Emergency Department.

† % baseline refers to the norm for the individual, established by the clinician. This may be% of standardized norms or % patient's personal best.

Care in a Hospital-Based Emergency Department

The discussion in this section accompanies Chart 9.

General Principles

Care should be expeditious and should be based upon following general principles.[1] Severe exacerbations of asthma are potentially life threatening; the patient with acutely severe asthma (see Figure 8-1) should be managed with the same sense of urgency as a 50-year-old person with crushing substernal chest pain suspected of having myocardial ischemia.

The principal goal of treatment is rapid relief of airflow obstruction. In a small percentage of patients with particularly severe disease, correction of marked hypoxemia is of paramount importance and is undertaken in parallel with the reversal of airflow obstruction.

The severity of airflow obstruction cannot be accurately judged by patient symptoms and physical examination alone. Measurements of airflow obstruction (by spirometry or by peak flow meter) are an integral part of the assessment of disease severity and of the response to therapy in any patient over 5 years of age.

Reversal of airflow obstruction is most effectively achieved by the repetitive administration of beta$_2$-agonist bronchodilators early in the course of an asthma exacerbation. Inhalation is the preferred route of administration.

It has not been demonstrated that theophylline in the first 4 hours of treatment provides any additional benefit to optimal inhaled beta$_2$-agonist therapy.

Systemic corticosteroids speed the resolution of severe exacerbations and should be administered early in the course of treatment to patients who fail to respond rapidly to beta$_2$-agonist bronchodilators.[2]

Unpleasant side effects (e.g., palpitations, tremulousness, sense of inner raciness, headache) are common with intensive therapy of asthma, but injurious adverse reactions (e.g., significant cardiac arrhythmias or myocardial ischemia) are rare.

Initial Assessment

A brief history pertinent to the exacerbation should be obtained. Important questions to ask include:

- Time of onset and cause of present exacerbation of disease.
- Severity of symptoms, including exercise limitation and disturbance of sleep.
- All current medications, time of last administered medication, and any recent use of systemic corticosteroids.
- Prior hospitalizations and emergency department visits for asthma.
- Prior episodes of respiratory insufficiency due to asthma (loss of consciousness or intubation and mechanical ventilation).
- Significant prior cardiopulmonary disease.

A brief cardiopulmonary examination should be performed, with emphasis on findings relevant to assessing the severity of the exacerbation (see Figure 8-1) or to identifying complications (e.g., pneumonia, atelectasis, pneumothorax, and pneumomediastinum). Assessment of the overall status of the patient should include alertness, color, respiratory distress, and fluid status. Findings that predict the presence of severe airflow obstruction include:

- Pulsus paradoxus (≥12 mm Hg fall in systolic blood pressure during inspiration).
- Use of accessory muscles of respiration (i.e., sternocleidomastoid muscles).
- Diaphoresis and refusal to recline on a stretcher or bed with the head elevated at <30°.[1]

Auscultation should be performed; recognize, however, that wheezing is an unreliable sign of the degree of airflow obstruction. In rare cases, extremely severe obstruction may be accompanied by a "silent chest."[3]

Figure 8-1
Emergency Department Findings of Acutely Severe Asthma in Adults

Symptoms/Historical Data
Severe breathlessness, cough, chest tightness, and wheezing
Difficulty walking 100 feet or more
Speech fragmented by rapid breathing
Syncope or near syncope

Physical Findings
Paradoxical pulse (≥12 mm Hg)
Use of accessory muscles of respiration
Diaphoresis; inability to lie supine
Heart rate >120 beats/min
Respiratory rate >30 breaths/min

Expiratory Flow
FEV_1 or PEFR <30-50% baseline (predicted or personal best, as determined by the clinician)
Failure of PEFR to improve at least 10% after initial treatment

Oxygenation
PO_2 <60 mm Hg or O_2 saturation <90%

Ventilation
PCO_2 ≥40 mm Hg

Laboratory studies, such as a complete blood count (CBC) with differential, sputum culture, and chest x-ray are not needed for the initial assessment of an acute asthma exacerbation, and their performance should not be permitted to delay therapy.

Measurement of airflow obstruction should be made using one of the following techniques:

Peak expiratory flow rate (PEFR) measured with a peak flow meter.

One-second forced expired volume (FEV_1) determined by spirometry.

These tests give comparable results and are equally acceptable. PEFR may be preferred for those patients who have difficulty performing the FEV_1 maneuver during an acute exacerbation. It is strongly emphasized that both measurements require (a) patient cooperation in making a maximal expiratory effort and (b) coaching by a person trained in making these measurements. Measurements obtained without meeting these criteria will be erroneous and may lead to errors in assessment and management.

Decision making based on the measured obstruction of airflow presumes that, when asymptomatic, the asthma patient has normal or near-normal lung function. Some asthma patients, most often those adults with longstanding and severe disease, may have significant fixed airflow obstruction even when symptomatically well. Knowledge of this fixed airflow obstruction during asymptomatic periods is useful in interpreting lung function measurements made during the acute exacerbation.

Arterial blood gas determination is rarely necessary prior to initiation of treatment. Only patients with a FEV_1 or PEFR <25 percent of predicted or with other signs of severe airflow obstruction are at risk for significant hypercapnia or acidosis.[4] An exception might be the patient in extremis who cannot perform pulmonary function tests or for whom intubation and mechanical ventilation are being considered; in this situation, arterial blood should be sampled while initial treatment is being given.

Initial Treatment

Initial treatment focuses on the administration of bronchodilators.[5,6] Inhalation of selective $beta_2$-agonist bronchodilators by nebulization is favored for both children and adults. Figure 8-2 (at the end of this section) and Figure 8-5 (at the end of the next section) show recommended doses.

It is recognized that delays in setting up nebulizer systems occur in some emergency services. Long delays are unacceptable. Restructuring emergency services where necessary is favored to ensure rapid availability of nebulizer systems. This goal can be achieved by training emergency department nurses to set up nebulizer systems or by having a specific room or rooms designated for this purpose with the equipment readily available.

Inhaled $beta_2$-agonist bronchodilators begin to act in less than 5 minutes. The duration of action in acutely severe asthma is unknown and probably varies with the severity of disease. Repetitive administration every 20 minutes for at least 1 hour is safe and produces incremental bronchodilation with each dose. Failure of PEFR or FEV_1 to respond more than 10 percent indicates deteriorating asthma.

In general, initial treatment should consist of three doses of nebulized $beta_2$-agonist bronchodilator administered within 60-90 minutes.

Fewer doses may be appropriate in patients with mild airflow obstruction who respond quickly to the initial dose and in whom adverse side effects outweigh the benefits of a full three treatments. However, for most patients, administration of a single dose with reevaluation of the patient 60 or more minutes later constitutes inadequate care.

Some (although not all) recent investigations suggest that $beta_2$-agonist bronchodilators administered from metered-dose inhalers (3-6 puffs per treatment) using spacer devices achieve bronchodilation equivalent to that effected by nebulization.[7] Further confirmation is required before this mode of inhaled $beta_2$-agonist bronchodilator delivery can be considered standard care in the emergency department.

Subcutaneous administration of $beta_2$-agonist bronchodilators is an alternative initial treatment regimen (see Figures 8-2 and 8-5 for doses). However, bronchodilation may be somewhat less than with inhalation, side effects may be greater, and the injections may be painful.

Immediate administration of intravenous corticosteroids (e.g., methylprednisone, 80-125 mg by intravenous bolus) may be warranted in some patients with very severe exacerbations of asthma in whom no improvement is observed after the initial dose of $beta_2$-agonist, or in those patients who developed an exacerbation despite the regular use of oral corticosteroids.

Administration of Supplemental Oxygen

Supplemental oxygen, usually administered by nasal cannulae (e.g., 2 L/min), or by mask in children, should be given to hypoxemic patients (arterial PO_2 <60 mm Hg, arterial oxygen saturation <90 percent). In many emergency services, the presence of arterial desaturation can be assessed noninvasively with pulse oximetry.

The presence of hypoxemia correlates poorly with the severity of airflow obstruction and cannot be accurately predicted based on measurement of PEFR or FEV_1.

Arterial oxygen tension will vary over time and in response to beta$_2$-agonist therapy. Beta$_2$-agonist bronchodilators may cause a transient, mild fall in arterial oxygen that can be corrected with supplemental oxygen.

In the absence of continuous arterial oxygen monitoring, it is best to administer supplemental oxygen to all patients.

Respiratory Failure

Patients with persistent respiratory distress and a PCO_2 that continues to rise despite appropriate therapy are at risk for respiratory failure. In general, intubation and mechanical ventilation are indicated for those patients whose PCO_2 exceeds 50 mm Hg and continues to rise despite therapy.

The apneic patient requires immediate intubation and mechanical ventilation. If effective mechanical ventilation cannot be achieved because of extremely high airway resistance, it may be necessary to administer beta$_2$-agonist bronchodilators intravenously or as a liquid squirted endotracheally. Whenever possible, administration of a nebulized beta$_2$-agonist bronchodilator via the endotracheal tube is the preferred route. In adults, intravenous administration of isoproterenol carries a risk of myocardial injury resulting from ischemia or infarction; and endotracheal administration without nebulization may provide suboptimal distribution of the medication.

Repeat Assessment

Repeated assessment should be performed after the initial dose of bronchodilator in the patient with extreme distress and in all patients after three doses of medication (60-90 minutes after initiating treatment). Repeat evaluation should include:

- History (particularly, the patient's sense of dyspnea).
- Physical examination (including vital signs and chest examination).
- Measurement of lung function by spirometry or by peak flow meter.

Arterial blood gases should be performed in patients with the following characteristics:

- Obvious hypoventilation.
- Too breathless to speak.
- Severe distress after the initial treatment.
- Cyanosis.
- FEV_1 or PEFR $\leq$25 percent of predicted after the initial treatment. In the absence of medications or chronic respiratory disease in addition to asthma, hypercapnia is rare among acutely ill asthma patients with FEV_1 or PEFR >25 percent of predicted.

A CBC is appropriate in febrile patients and patients with purulent sputum production. A CBC should be obtained before administration of systemic corticosteroids or epinephrine because steroid-induced demargination of white blood cells may cause leukocytosis.

A chest radiograph is warranted in patients suspected of a complication to evaluate for atelectasis, pulmonary infiltrates, pneumothorax, or pneumomediastinum. In general, however, chest x-rays are overused in the treatment of acute asthma and contribute little useful information.[8]

Serum theophylline concentration should be determined in patients taking a theophylline-containing preparation prior to presentation, if a recent theophylline level is not available.

Interpreting the Response to Initial Treatment

- **Good response.** Patients with a good response can be discharged from the emergency service with a low likelihood of relapse (i.e., recurrent severe symptoms within 2-3 days). Some patients, particularly those with risk factors for life-threatening asthma (as noted earlier), may benefit from initiation of a brief course of oral corticosteroid. Patients should be observed for 30-60 minutes after the last dose of beta$_2$-agonist to ensure stability of the response prior to discharge.
  - —History: Patient free of wheezing and shortness of breath.
  - —Physical examination: Chest free of wheezes on auscultation.
  - —PEFR or FEV_1 $\geq$70 percent of predicted.
- **Incomplete response.** Patients with an incomplete response require continued treatment in the emergency department.
  - —History: Persistent wheezing or shortness of breath.
  - —Physical examination: Wheezes present on auscultation.
  - —PEFR or FEV_1 >40 percent and <70 percent of predicted.
- **Poor response.** Patients with a poor response require continued treatment with close observation up to 4 hours. These patients should be evaluated for the possible need for hospitalization.
  - —History: Complaint of persistent, marked wheezing and shortness of breath.
  - —Physical examination: Chest with diffuse wheezes on auscultation; tachypnea, pulsus paradoxus, accessory respiratory muscle use, and other signs of severe disease (see above) may still be present.
  - —PEFR or FEV_1 $\leq$40 percent of predicted.

Patients with a poor response and PCO_2 $\geq$40 mm Hg after initial treatment should be admitted to the hospital promptly, preferably to an intensive care unit.

Continuation of Treatment
Nebulized beta$_2$-agonist treatments are given frequently (see Charts 8, 9, and 10 and see also dosage tables for children and adults in Figures 8-2 and 8-5).

Adults with a poor response to initial treatment (as just described) may benefit from subcutaneous administration of beta$_2$-agonist bronchodilators.[9]

Patients with a poor response after 1 hour of initial treatment should receive oral or parenteral corticosteroids.

■ The optimal dose of corticosteroids is not known. An initial dose of methylprednisolone 80-125 mg intravenously in adults, and 1-2 mg/kg oral or parenteral methylprednisolone in children is generally recommended. It is recognized that other corticosteroid preparations and other routes of administration (i.e., oral) may be equally effective.

■ The time to peak effect of systemic corticosteroids in asthma is uncertain; it is thought to be a matter of hours, possibly 6-12 hours.

■ *Potential* side effects from the acute administration of systemic corticosteroids are discussed in the Pharmacologic Therapy section of Chapter 4. If a patient has diabetes, peptic ulcer, hypertension, or emotional disorder, systemic corticosteroids may accentuate the condition. These patients should be monitored accordingly.

Patients with an incomplete response should also be considered for systemic corticosteroids. Factors favoring treatment with systemic corticosteroids include long duration of symptomatic asthma prior to presentation (subacute exacerbation), chronic use of multiple antiasthma medications at the time of presentation, chronic use or recently discontinued use of oral corticosteroids, frequent or recent emergency department visits or hospitalizations for asthma, past history of respiratory failure due to asthma, and, in children, viral-infection-induced asthma.

Repeated Assessments
Repeated assessment of the patient's response to treatment should be made at least hourly. These assessments should include history and physical examination and pulmonary function testing.

Patients may have worsening airflow obstruction while under care in the emergency department. Clinicians must be alert to evidence of deterioration (history, physical examination, PEFR or FEV_1, and where necessary, arterial blood gases). The patient who is deteriorating despite the therapies recommended above should be admitted promptly to the hospital.

Other Therapies in the Emergency Department

■ **Bronchodilators**

—*Methylxanthines*

- When used alone, intravenous aminophylline is three to four times less effective in relieving airflow obstruction than repetitively administered beta$_2$-agonist bronchodilators in both adults and children.[10]
- When used in combination with repetitively administered beta$_2$-agonist bronchodilators, intravenous aminophylline causes increased adverse side effects without effecting additive bronchodilation.[4,9]
- Theophylline may play a significant role in the asthma patient's chronic (outpatient) treatment program. Patients receiving chronic theophylline therapy who present to the emergency department with an acute exacerbation of asthma and a subtherapeutic theophylline level may benefit from oral theophylline or intravenous aminophylline which will raise the serum theophylline concentration.
- It is emphasized that in adults or children treated with repetitive administration of beta$_2$-agonist bronchodilators, methylxanthines play no significant role in the acute relief of airflow obstruction. The patient's serum theophylline level is not important in achieving immediate bronchodilation.

—*Anticholinergics*

- In some, but not all reports, nebulized ipratropium bromide solution (500 g) provides incremental bronchodilation when used in combination with nebulized beta$_2$-agonist bronchodilators. The additive bronchodilation, when observed, was small (approximately 10 percent).[4,15]
- Ipratropium bromide solution for nebulization is not currently available for use in the United States. Benefit has not been shown for ipratropium bromide by metered-dose inhaler.

■ **Antibiotics**

—Respiratory tract infections that trigger exacerbations of asthma are usually viral. Unlike chronic bronchitis and emphysema, routine use of antibiotics is not indicated for adults or children with acutely severe asthma.

—In adult patients with fever and purulent sputum, in the absence of pneumonia, empiric antibiotic coverage (e.g., with ampicillin, tetracycline, erythromycin, or trimethoprim-sulfamethoxasole) may be warranted. The possibility of sinusitis should be considered in both adults and children and should be treated with antibiotics if suspected.

—Because of the presence of eosinophils, the gross appearance of asthmatic sputum may mimic purulent sputum. Sputum purulence should be judged on the basis of microscopic examination of the sputum to identify the presence of polymorphonuclear leukocytes.

■ **Hydration**

—In adults and children with normal access to water and liquid beverages, intravenous or oral administration of large volumes of fluids (hydration) does not play a role in the management of acutely severe asthma.

—No evidence is available to support the concept that large volumes of fluids taken enterally or parenterally favorably alter the consistency or viscosity of asthmatic sputum in such a way as to promote its clearance.

—Infants and young children may become dehydrated more rapidly from increased respiratory rate and decreased intake. Assessment of hydration should be made (urine output, urine specific gravity, mucus membrane moisture, electrolytes) and appropriate corrections provided.

Patient Discharge From the Emergency Department

Release of the patient from the emergency department depends on the patient's response to treatment.

■ **Good response.** Patients who achieve symptom relief, are free of wheezes on chest auscultation, and have PEFR or FEV_1 ≥70 percent of predicted (or of their known best value when asymptomatic) can be discharged home from the emergency service. A 30-60 minute period of observation after the last dose of bronchodilator will assure stability of response before discharging a patient.

■ **Poor response.** Patients who have persistent symptoms, diffuse wheezes audible on chest auscultation, and a PEFR or FEV_1 ≤40 percent of predicted should be admitted to the hospital.

■ **Incomplete response.** Decisions regarding hospitalization of patients achieving only a partial response to treatment in the emergency department need to be individualized. An incomplete response is characterized by some persistence of symptoms of the asthma exacerbation, some wheezes on chest auscultation, and a PEFR or FEV_1 <70 percent and >40 percent of predicted. Factors favoring hospitalization include:

—PEFR or FEV_1 values close to the lower end of the range of intermediate.

—Recent emergency department visit or hospitalization for asthma.

—Multiple emergency department visits or hospitalizations for asthma within the past year.

—Past history of respiratory failure due to asthma.

—Prolonged (≥1 week) increase in asthma symptoms prior to presentation for treatment of this exacerbation of asthma.

—Use of multiple antiasthma medications at the time of presentation for treatment of this exacerbation of asthma.

—Use of systemic corticosteroids at the time of presentation for treatment of this exacerbation of asthma.

—Infant <1 year of age with incomplete response and viral bronchiolitis.

—Adequate followup care at home not available.

—Depression, psychosis, or other serious psychiatric disorder.

■ **Other considerations.** Prolonged detention (over 4 hours) of adult and childhood asthma patients in the emergency department awaiting a good response to treatment is to be avoided.

Patients with complications of their asthma, or its treatment, may require hospitalization on the basis of the complications. Examples include patients with acute pneumonia, lobar or multilobar atelectasis, pneumothorax, and intractable vomiting.

Recommendations at Discharge

No single treatment program can be recommended for all patients discharged home from the emergency department following treatment of an asthma exacerbation. However, the following guidelines are considered important general principles.

An asthma exacerbation does not end at the time of discharge from the emergency department. In almost all instances, there will be residual abnormalities of lung function.[16] In addition, the bronchodilator activity of $beta_2$-agonist bronchodilators is brief (≤4 hours). Therefore, it is of utmost importance that at least a 3-5 day treatment regimen for the acute exacerbation be prescribed for the patient to continue after discharge. The treatment regimen will frequently include a course of oral corticosteroids. For patients who developed an exacerbation of their asthma while taking antiasthma medications, this continued treatment regimen should generally represent an intensification of their treatment program, not simply a resumption of prior treatments.

A course of oral corticosteroids reduces the rate of recurrent severe asthma symptoms and return emergency department visits among patients discharged home from the emergency department.[17] In general, all

patients with an FEV_1 or PEFR ≤70 percent of baseline (or best value when asymptomatic) should receive a course of oral corticosteroids. All patients at increased risk for potentially life-threatening deterioration should receive a course of corticosteroids.

Close medical followup following an acute asthma exacerbation is important not only to assure resolution of the acute exacerbation but also to review the long term medication plan because an acute exacerbation requiring emergency department treatment may well indicate a need for more preventive daily therapy. A followup medical appointment should be made when the patient is discharged from the emergency department. The patient should be assessed within 48-72 hours of discharge.

Patient education is an important part of the process of patient disposition from the emergency department. Education should include review of discharge medications and the importance of receiving care in an outpatient regular-care setting. Patients may be issued a peak flow meter at the time of their discharge and instructed to measure peak expiratory flow rate twice a day (see Chapter 2, Objective Measures of Lung Function). This information should be reported to their continuing care clinician at the followup visit.

Hospital Management of Severe Exacerbations of Asthma

The discussion in this section accompanies Chart 10.

General Principles

Nearly all patients admitted to the hospital for management of acutely severe disease will have moderate to severe airflow obstruction refractory to initial intensive bronchodilator treatment (status asthmaticus). Care of these patients requires close medical attention (including serial assessment of lung function) by skilled nurses, respiratory therapists, and physicians. It is recommended that all patients admitted to an intensive care unit should have consultation with an asthma specialist; consultation should also be considered for all patients with multiple hospital admissions.

Patients may underestimate the severity of their own disease. Likewise, physicians may misjudge the severity of airflow obstruction if they rely solely on the history and physical examination. Daily serial lung function measurements (peak expiratory flow rate determination or spirometry) before and after bronchodilator therapy are recommended to assess the severity of an asthma exacerbation, to guide therapy, and to determine the patient's response to therapy.

Clinicians must remain alert to the possibility of sudden or rapid deterioration in the patient's condition, which may result from bronchoconstriction, mucous plugging, or, less commonly, pneumothorax. Patients at particular risk for life-threatening deterioration may have one or more of the following characteristics:

- Improvement over initial PEFR or FEV_1 measured in the emergency department of ≤10 percent.
- FEV_1 or PEFR ≤25 percent of predicted.
- PCO_2 ≥40 mm Hg.
- Wide daily fluctuations in PEFR or FEV_1.
- Prior history of life-threatening exacerbations of asthma (i.e., hypercapnia or loss of consciousness).
- Infants less than 1 year of age.

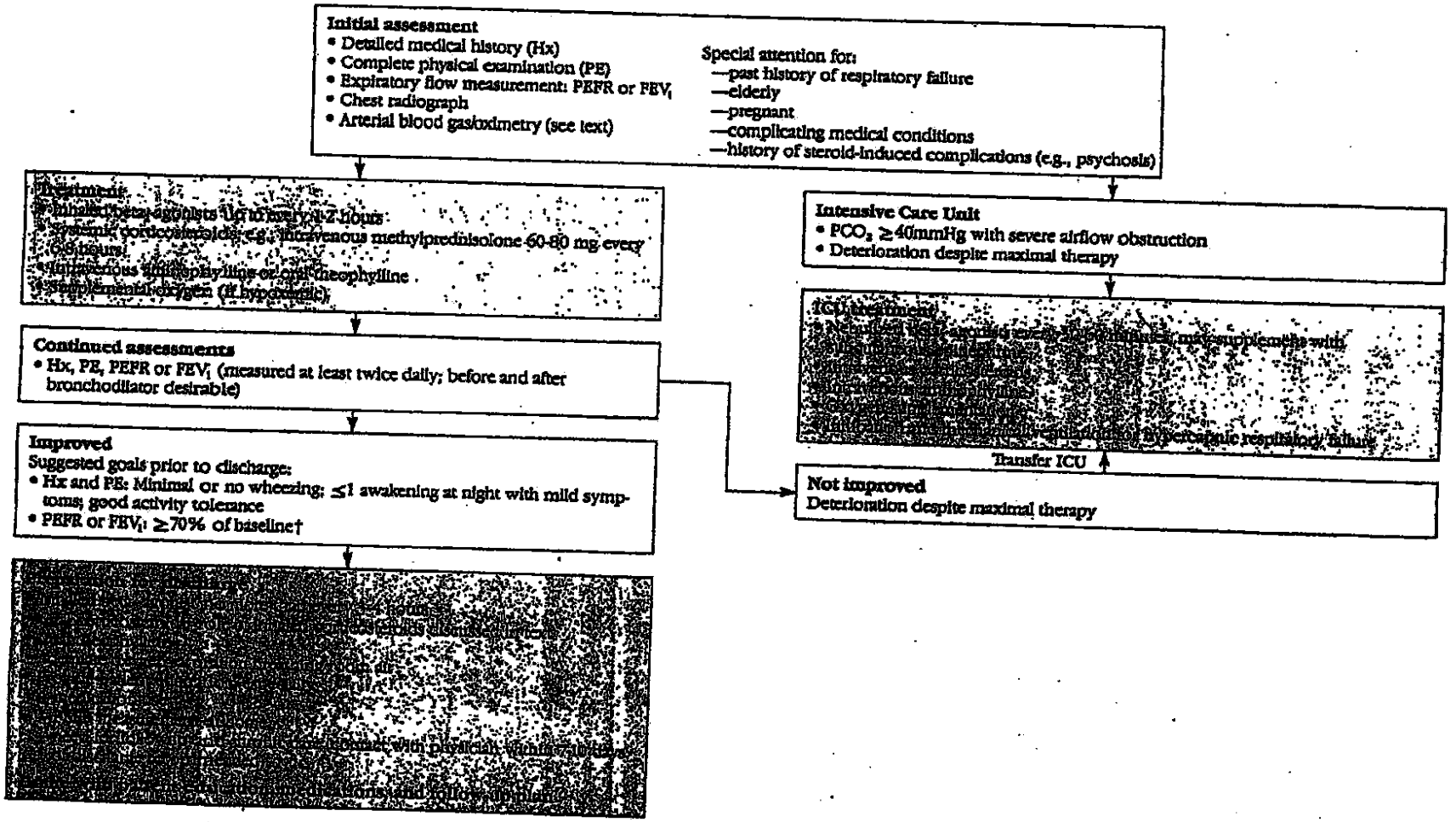
General Guidelines to Treatment

The principal therapies for hospital management of asthma are inhaled $beta_2$-agonist bronchodilators, systemic corticosteroids (recommended for all hospitalized patients), and methylxanthines.

- **$Beta_2$-agonists**
  - —Inhaled $beta_2$-agonists constitute the mainstay of bronchodilator therapy for severe exacerbations of asthma. In the doses routinely used, the inhalation route of administration of $beta_2$-agonists has fewer side effects and is possibly more effective than subcutaneous $beta_2$-agonists. In recent years, nebulization of a $beta_2$-agonist solution into a wet aerosol has been the standard method of delivery for inhalational use in the hospital. Recent studies have raised the possibility that $beta_2$-agonist delivery from a pressurized metered-dose inhaler (MDI) used with a spacer device may be equally effective as nebulization into a wet aerosol. The optimal dose of $beta_2$-agonist by MDI with a spacer is not known; the dose may need to be titrated to the individual patient's response. Because of difficulty in coordination and cooperation, administration of $beta_2$-agonist by MDI is not recommended for the hospitalized child.
  - —The frequency of $beta_2$-agonist administration varies according to the severity of the patient's asthma symptoms and the occurrence of adverse medication side effects. In severely ill adult

Acute Exacerbations of Asthma in Adults

Hospital Management



†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best.

patients, hourly administration may be necessary, and in children continuous administration of inhaled beta$_2$-agonists may be necessary (see Figures 8-2 and 8-5 for dosages).

■ **Corticosteroids**

—Systemic corticosteroids speed the resolution of severe asthma exacerbations refractory to bronchodilator therapy and should be given to all adults and children admitted to the hospital with acutely severe asthma.

—Results of several studies indicate that the oral administration of systemic corticosteroids, specifically methylprednisolone, is as effective as intravenous administration. Pending additional investigations, however, it is recommended that therapy with intravenous corticosteroids be instituted in hospitalized patients, since this approach is known to be effective.

—The optimal dose of systemic corticosteroids is not known. (See Figures 8-2 and 8-5 for recommended doses.)

■ ***Methylxanthines***

—Instituting therapy with oral or intravenous methylxanthines in adults and children hospitalized with asthma is recommended.

—Studies on the emergency department management of asthma indicate that methylxanthines do not significantly enhance the bronchodilator response to beta$_2$-agonists when the latter are given repetitively at short intervals. However, when the dose and frequency of inhaled beta$_2$-agonists are reduced, methylxanthines and beta$_2$-agonists may effect additive bronchodilation.

—Methylxanthines are at present part of the routine care of patients hospitalized with severe asthma, although the precise benefit that they afford remains to be defined. It may be that as the frequency of administration of inhaled beta$_2$-agonists is reduced (e.g., overnight or secondary to adverse side effects), methylxanthines prolong or sustain the bronchodilator response between doses.

—Oral theophylline and intravenous aminophylline are equally effective when the serum theophylline concentrations achieved by the two routes of administration are identical.

—Patients who take theophylline as part of their maintenance therapy for asthma and who are not vomiting can simply be maintained on oral therapy with a sustained-release preparation. The dose is adjusted according to the serum concentration of theophylline. Increments in serum concentration of theophylline can be achieved rapidly by the oral route using the alcohol-based elixir of theophylline.

■ **Oxygen**

—Supplemental oxygen should be administered to the hypoxemic patient to achieve an arterial oxygen saturation of ≥90 percent.

—Because arterial oxygen saturation may intermittently decline during the course of the acute illness and in response to beta$_2$-agonist therapy, the criteria for oxygen supplementation should be more liberal (e.g., arterial oxygen saturation <92 percent) among patients at risk for adverse consequences of transient hypoxemia (e.g., patients who are pregnant, elderly, or have known coronary artery disease).

—Arterial oxygen saturation should be measured in all acutely ill adult and child asthma patients admitted to the hospital, preferably by oximetry.

■ **Other Therapies**

—*"Hydration"*

In adults and children without clinical signs of dehydration, administration of large amounts of fluids intravenously or by mouth is not recommended. There is no evidence available to suggest that the viscosity or clearance of airway secretions can be favorably altered in asthma by this approach.

—Chest Physical Therapy

In general, among patients with normal respiratory muscle strength and effective cough, chest physical therapy is not beneficial and may be unnecessarily stressful for the acutely breathless patient. However, in selected adult and child patients who manifest severe mucous hypersecretion as part of their asthma exacerbation, postural drainage, chest vibration and percussion, and other techniques of chest physical therapy may, at times, be beneficial.

■ **Mucolytics**

—There is no available evidence to support the use of mucolytic agents (e.g., acetylcysteine, potassium iodide, and others) in severe exacerbations of asthma in either adults or children. These agents may worsen cough or airflow obstruction and should be avoided.

■ **Sedation**

—Because of the respiratory depressant effects of anxiolytic and hypnotic drugs, these sedating medications should be ***strictly avoided*** in acutely ill adult and childhood asthma

patients. The anxiety that accompanies severe breathlessness should be treated with therapies that reduce airflow obstruction and correct hypoxemia.

- **Antibiotics**
  - —Bacterial and mycoplasmal respiratory infections are thought to contribute only infrequently to severe exacerbations of asthma. It is generally recommended that the use of antibiotics be reserved for those patients with purulent sputum (purulent appearing by virtue of polymorphonuclear leukocytes, not eosinophils), especially when combined with fever.
- **Anticholinergics**
  - —Ipratropium bromide in the currently available metered-dose inhaler form does not appear to benefit patients receiving intensive bronchodilator therapy with beta$_2$-agonists and methylxanthines. In contrast, ipratropium bromide nebulizer solution has been of some benefit, but it is not currently available in the United States.

Recommendations for Assessment

Objective measurements of airflow obstruction (PEFR determination or spirometry) should be made throughout the patient's hospital course, preferably at least twice daily (see Chart 10). The precise timing of the measurement is less important than the regular performance and recording of the measurement.

Arterial blood gas measurements are not necessary in all patients. They should be performed to evaluate arterial PCO_2 in patients admitted to the hospital with severe respiratory distress in whom the PEFR or FEV_1 is <25 percent of predicted. Patients with severe respiratory distress and PCO_2 ≥40 mm Hg require repeated arterial blood gas measurements to monitor their response to treatment; an arterial line in an intensive care setting is the preferred approach. Pulse oximetry is the preferred method to assess for arterial oxygen desaturation.

Chest radiographs remain part of the routine care of asthma patients admitted to the hospital with severe exacerbations, although the frequency with which clinically unsuspected complications are detected in this setting is probably low.

Recommendations for Treatment

- Nebulized selective beta$_2$-agonists should be administered frequently by wet aerosol. The frequency of administration can be increased to hourly in adult patients with severe airflow obstruction and brief benefit from the bronchodilator treatment; it can be reduced to every 3-4 hours in patients with less severe airflow obstruction who experience significant medication side effects (see Figure 8-2 for dosage). In infants and children, the beta$_2$-agonists may be given continuously (see Figure 8-5 for dosage). Close supervision with electrocardiographic monitoring is recommended.
- Methylprednisolone 60-80 mg every 6-8 hours is given by intravenous bolus in adults. The low end of this dose range is generally favored. In children, the dose is 1-2 mg/kg every 6 hours for the first 24 hours and then tapering.
- Methylxanthines generally should be given to all hospitalized adults and children with asthma (see Figures 8-2 and 8-5 for dosage recommendations). The target serum concentration for theophylline should be μ5-15 g/mL with 20 μg/mL as the upper limit. It is not necessary to maintain the serum concentration as close as possible to 20 μg/mL.

Treatment of Impending Respiratory Failure

Adults and children with severe asthma and an arterial PCO_2 ≥40 mm Hg after intensive therapy are at risk for respiratory arrest and should receive their care in an intensive care unit.

Indications for intubation and initiation of mechanical ventilation depend not only on the arterial PCO_2 but also on the entire clinical setting. The patient's response to therapy (has there been gradual improvement or deterioration?), the respiratory rate, and the presence of respiratory muscle fatigue as manifested by paradoxical inward movement of the abdomen on inspiration are important clinical parameters. In general, if there is steady deterioration despite intensive therapy for asthma, the patient should be intubated and mechanically ventilated when the PCO_2 is ≥50 mm Hg and rising.

Frequent administration of nebulized beta$_2$-agonist bronchodilators is the mainstay of therapy. Treatments may need to be given as often as every 20-30 minutes for brief periods in patients with impending respiratory failure and by continuous inhalation in children. Subcutaneous administration of beta$_2$-agonists may be used to supplement inhaled therapy in adults.

Intravenous administration of beta$_2$-agonist bronchodilators (isoproterenol or terbutaline) in adult asthma patients with impending respiratory failure should be avoided because of the high risk of myocardial injury.

Intravenous isoproterenol is not generally recommended for children. The possibility that intravenous beta$_2$-agonists (albuterol or terbutaline) may offer additional bronchodilation for children is a subject of current debate.

Treatment of Respiratory Failure and Respiratory Arrest

Adult and pediatric patients with respiratory arrest due to severe asthma should be immediately intubated and receive mechanically assisted ventilation.

Intubation may be difficult and should only be performed by a physician skilled in intubation.

As part of the resuscitation effort of the apneic patient, beta$_2$-agonist bronchodilators may be given intravenously and via the endotracheal tube until adequate ventilation can be achieved mechanically.

Management of the intubated and mechanically ventilated patient with asthma will not be discussed here in detail. However, two important principles to follow are:

- Beta$_2$-agonist bronchodilators can be nebulized inline into the inspiratory circuit of the ventilator system and remain the mainstay of bronchodilator therapy.
- The immediate goal of mechanical ventilation should not necessarily be restoration of the arterial PCO_2 to normal. The combination of respiratory rate and tidal volume necessary to achieve eucapnia may generate excessive peak inflation pressures and lead to alveolar gas trapping and overdistention, exposing the patient to an unacceptably high risk of barotrauma (pneumothorax and pneumomediastinum). The preferred approach is to choose a combination of respiratory rate and tidal volume that generates peak inflation pressures ≤ 40 cm H_2O and to tolerate an elevated arterial PCO_2 if it ensues. The arterial PCO_2 will gradually be corrected to normal as the underlying airflow obstruction resolves. This concept of "mechanically controlled hypoventilation" in respiratory failure resulting from severe asthma helps limit iatrogenic morbidity.[28]

Preparing the Patient for Discharge

Prior to discharge of the patient from the hospital, the medication regimen should be adjusted to a program of oral and/or inhaled medications. In patients who received intravenous aminophylline or corticosteroids these medications must be changed to the oral route of administration. Patients receiving nebulized beta$_2$-agonists by wet aerosol may be changed to the metered-dose inhaler delivery system, with or without a spacer, or a dry powder inhaler.

The precise time at which the transition to an outpatient or post-discharge regimen should be made is poorly defined. There is considerable evidence to suggest that oral corticosteroids and theophylline in comparable doses to intravenous corticosteroids and aminophylline, respectively, produce identical degrees of improvement in lung function. Thus, the precise timing is probably of little importance unless accompanied by a significant adjustment in dose (as is often the case for the transition from intravenous to oral corticosteroids). The general approach has been to wait until the patient is minimally symptomatic from asthma and has no or minimal wheezing on chest examination. This timing is likely to correspond to a PEFR or FEV_1 value between 60 percent and 70 percent of predicted (or of the best value at baseline).

- The recommended oral dose of theophylline is calculated in the dosage tables (see Figures 8-2 and 8-5).
- When changing from intravenous to oral corticosteroids in adults, it is generally recommended that prednisone (or methylprednisone) be started at 60 mg/day as a single or divided dose. The transition may represent a significant dose reduction in corticosteroids; patients should be observed for possible deterioration during the 24 hours after this adjustment.
- For adult patients, inhaled corticosteroids may be initiated at the first followup visit during the prednisone taper. An alternative strategy that may enhance patient adherence would be to begin inhaled corticosteroids along with the oral corticosteroid therapy at the time of discharge from the hospital.
- Most adult patients who have received nebulized beta$_2$-agonist bronchodilators by wet aerosol in the hospital will be discharged with a beta$_2$-agonist bronchodilator by metered-dose inhaler or dry powder inhaler, to be used no more than every 3-4 hours. The ability to maintain good lung function using the metered-dose route of delivery (with or without a spacer) should be confirmed prior to discharge. If, after 3-5 days of discharge, the patient still requires frequent beta$_2$-agonist, consideration should be given to additional anti-inflammatory therapy.
- In patients who received supplemental oxygen during their hospitalization, the adequacy of their arterial oxygen saturation while breathing room air should be confirmed prior to discharge. The preferable method is pulse oximetry.
- Most patients over 5 years of age would benefit by being discharged with a peak flow meter and given instructions to measure and record PEFR twice daily and to report these measurements to their continuing care clinician at the followup visit.
- All patients should receive education about discharge medication, peak flow meters, and the importance of a followup medical visit in an outpatient regular-care setting.

Figure 8-2

Dosages of Drugs in Acute Exacerbations of Asthma in Adults

Inhaled Beta-Agonists

- Albuterol 2.5 mg (0.5 cc of a 0.5% solution, diluted with 2-3 cc of normal saline); or
- Metaproterenol 15 mg (0.3 cc of a 5% solution, diluted with 2-3 cc of normal saline); or
- Isoetharine 5 mg (0.5 cc of a 1% solution, diluted with 2-3 cc of normal saline); or

Subcutaneous Beta-Agonists

- Epinephrine 0.3 mg s.q.; or
- Terbutaline 0.25 mg s.q.

Methylxanthines

Intravenous

—Aminophylline 0.6 mg/kg/hr by continuous infusion. Lean body weight should be used for these calculations in obese patients. In patients not previously receiving a methylxanthine, a loading dose (6 mg/kg) should be administered. The continuous infusion rate should be adjusted for factors that alter the metabolism of theophylline, including liver disease, congestive heart failure, cigarette smoking, and certain medications (e.g., erythromycin, cimetidine, and ciprofloxacin). The continuous infusion rate should be adjusted according to the serum theophylline level, which should be measured first approximately 6 hours after infusion begins.

- Oral

—Daily theophylline dose (mg) = total dose (mg) of aminophylline per 24 hours × .80.

—The dose of theophylline can be given as a sustained-release preparation in two divided doses or a once-daily preparation.

Corticosteroids

- Intravenous

—Methylprednisolone 60-80 mg i.v. bolus every 6-8 hours; or

—Hydrocortisone 2.0 mg/kg i.v. bolus every 4 hours; or

—Hydrocortisone 2.0 mg/kg i.v. bolus, then 0.5 mg/kg/hr continuous intravenous infusion.

- Oral

—A typical oral regimen that may be used as a substitute for intravenous corticosteroids might be prednisone or methylprednisolone 60 mg given immediately, then 60-120 mg per day in divided doses, tapered over several days at the discretion of the physician.

With improvement in the patient's condition, corticosteroids are usually tapered to a single daily dose of oral prednisone or methylprednisolone (e.g., 60 mg/day), or divided doses (e.g., 20 mg tid), then gradually further reduced over several days.

If the patient requires a prolonged course of oral corticosteroids, side effects may be minimized by a single a.m. dose given on alternate days.

Hospital Discharge

There are no prospectively validated criteria to guide the decision of when the asthma patient recovering from a severe exacerbation should be discharged from the hospital. Reaching the following goals prior to discharge are suggested:

- **History:** No or minimal wheezing; good exercise capacity; ability to sleep at night with less than one awakening resulting from mild asthma symptoms.
- **Physical examination:** No wheezes on auscultation.
- **Expiratory flow:** PEFR or FEV_1 ≥70 percent of predicted (or at personal best baseline value).

It is anticipated that at discharge patients will no longer exhibit wide (>30 percent) diurnal fluctuations in PEFR.

Following discharge, it will generally be necessary to reduce the dose of prednisone in a step-wise fashion over time (steroid taper). The precise dose schedule and duration of the taper will vary based on a number of factors, including:

- Duration of hospitalization (time required for resolution of the present exacerbation).
- History of systemic steroid use prior to admission.
- History of frequent recent hospitalizations or emergency department visits.
- History of life-threatening asthma.

During the period of steroid tapering following hospitalization, the asthma patient is at risk for recurrent severe morbidity from asthma. Thus, close medical followup during this period is mandatory.

Protocol for Management of Acute Exacerbations of Asthma in Children

Development of individualized crisis management plans tailored to the unique needs of specific patients is encouraged. The following strategies are provided as general guidelines considered applicable to most patients.

The general principles of the management of acute childhood asthma exacerbations are the same as for adults and are covered in the preceding section. The discussion in this section specifically refers to (1) the assessment of the child with asthma and (2) discussion of medical treatments outlined on the accompanying flow charts (Charts 11, 12, and 13). Special problems related to infants with acute airway obstruction are discussed in the next section.

Estimation of Severity of Exacerbation of Asthma in Children

In assessing the infant or child with an acute asthma exacerbation, several objective and subjective parameters may be used in combination to give the most accurate picture of the severity of the airway obstruction. These parameters are listed in Figure 8-3. It is often difficult for the physician and parent to determine the severity of the airway obstruction in the infant and small child with asthma. However, by using a combination of the parameters in Figure 8-3, a fairly accurate assessment can be made and treatment instituted promptly.

- **Respiratory rate** is variable in children and should be assessed when the child is at rest or sleeping as activity can markedly increase the respiratory rate of an infant or child (see Figure 8-4).[1]
- **Overall alertness** or response to environment and parents may help determine the level of fatigue of the child.
- **Dyspnea,** which is the parents' or physician's impression of the degree of the child's breathlessness, can help determine the degree of airway obstruction. This can be semiquantitated by having the child say a sentence with one breath or count to 10 with one breath. As the patient improves, he or she will be able to count higher or say more words without needing to take another breath.
- **Pulsus paradoxus** is the difference in fluctuation of systolic blood pressure between inspiration and expiration. The pressure falls with inspiration and rises with expiration. It can best be measured in children by a sphygmomanometer and stethoscope as the difference in systolic blood pressure between the pressure at which an observer first hears sporadic, faint pulse sounds and the pressure at which he or she hears all sounds.[2] No attempt should be made to correlate pulsus paradoxus with phase of respiration in small children. One limitation in children is that the heart rate is often so fast in small children that this is difficult to measure without an arterial line. However, if the pulsus paradoxus is >20 mm Hg, then moderate to severe obstruction is present.[2]
- **Accessory muscle use** correlates well with obstruction in children. It has been shown that the use of the sternocleidomastoid muscles correlates with a peak expiratory flow rate (PEFR) or FEV_1 of <50 percent of predicted.[3] In addition, parents and other health professionals can be taught to watch for intercostal retractions and other accessory muscle use. Flaring of the alae nasi exists when an enlargement of both nares occurs during inspiration. The appearance of flaring indicates that accessory muscles are being recruited for inspiration. It is an excellent sign of dyspnea.

Figure 8-3
Estimation of Severity of Acute Exacerbations of Asthma in Children*

Sign/Symptom	Mild	Moderate	Severe
Respiratory rate (see Fig. 8-4)	Normal to <1 standard deviation from the norm (S.D.) for age	Normal to <2 S.D. for age	Normal to >2 S.D. for age
Alertness	Normal	Normal	May be decreased
Dyspnea**	Absent or mild; speaks in complete sentences	Moderate; speaks in phrases or partial sentences	Severe; speaks only in single words or short phrases
Pulsus paradoxus	<10 mm Hg	10-20 mm Hg	20-40 mm Hg
Accessory muscle use	No intercostal to mild retractions.	Moderate intercostal retraction with tracheosternal retractions; use of sternocleidomastoid muscles	Severe intercostal retractions, tracheosternal retractions with nasal flaring
Color	Good	Pale	Possibly cyanotic
Auscultation	End expiratory wheeze only	Wheeze during entire expiration and inspiration	Breath sounds becoming inaudible
Oxygen saturation	>95%	90-95%	<90%
PCO_2	<35	<40	>40
PEFR	70-90% predicted or personal best	50-70% predicted or personal best	<50% predicted or personal best

Note: Within each category, the presence of several parameters, but not necessarily all, indicate the general classification of the exacerbation.

**For discussion of these parameters, see text.*

***"Parents' or physician's impression of degree of child's breathlessness.*

Figure 8-4
Respiratory Rates (Breaths/Minute) of Normal Children, Sleeping and Awake

Age	Sleeping			Awake			Mean Difference Between Sleeping and Awake
	No.	Mean	Range	No.	Mean	Range	
6-12 months	6	27	22-31	3	64	58-75	37
1-2 years	6	19	17-23	4	35	30-40	16
2-4 years	16	19	16-25	15	31	23-42	12
4-6 years	23	18	14-23	22	26	19-36	8
6-8 years	27	17	13-23	28	23	15-30	6

Source: Wising WW. The history and physical exam, in Kendig, Chernick (eds).: *Disorders of the Respiratory Tract in Children*. Philadelphia, W.B. Saunders, 1983, p. 63.

■ **Wheezing** indicates partial obstruction and may be caused by single or multiple points of narrowing within the airways. Wheezing is probably the least sensitive indicator of airflow obstruction. Usually a louder wheeze is felt to be a sign of greater airway obstruction; however, the patient may be so obstructed that he or she is not generating enough airflow to wheeze. Therefore, a quiet chest may indicate severe obstruction.

■ **Hypoxia** in acute asthma can result from ventilation/perfusion inequalities in the lung. One of the measurements that has predicted the need for hospitalization in asthma is an oxygen saturation of <91 percent in room air. This is easily measured with a pulse oximeter and can be used in small infants.

■ **PEFR** is the best objective measurement of airflow obstruction. PEFR quantitates the degree of obstruction and measures response of the patient to bronchodilator medication. It can be used with children 5 years or older. Since it requires only a short blast of air, PEFR can be used in the acutely obstructed child (see Chapter 2, Objective Measures of Lung Function).

Home Management

The discussion in this section accompanies Chart 11.

Many young patients who have moderately severe to severe asthma will have equipment and medications at home necessary for treating and monitoring an acute asthma exacerbation. In addition, patients who live in rural settings may, by necessity, have to manage an acute asthma exacerbation at home. The degree of care provided in the home depends on both the physician's and patient's experience and the availability of emergency care. For school-age children, a management plan for exacerbations occurring at school can be adapted from the home management plan (see Chapter 5, Patient Education).

The severity of the asthma exacerbation should be assessed on the basis of the general activity level of the child, the response of the child to his or her environment, pulse rate, respiratory rate, degree of airflow obstruction, and use of accessory muscles. In addition, PEFR measurements should be obtained in the child older than 5 years. The patient may be treated with inhalation of a selective $beta_2$-agonist (albuterol*) by compressor-driven nebulizer or with inhalations of a selective $beta_2$-agonist delivered by a metered-dose inhaler with or without a spacer device.

Following the first nebulizer treatment, the patient should be assessed for improvement in airflow movement, heart rate, respiratory rate, and PEFR. If the patient's PEFR has improved to >70 percent of predicted or personal best, the $beta_2$-agonists should be administered every 3-4 hours with continued assessment.

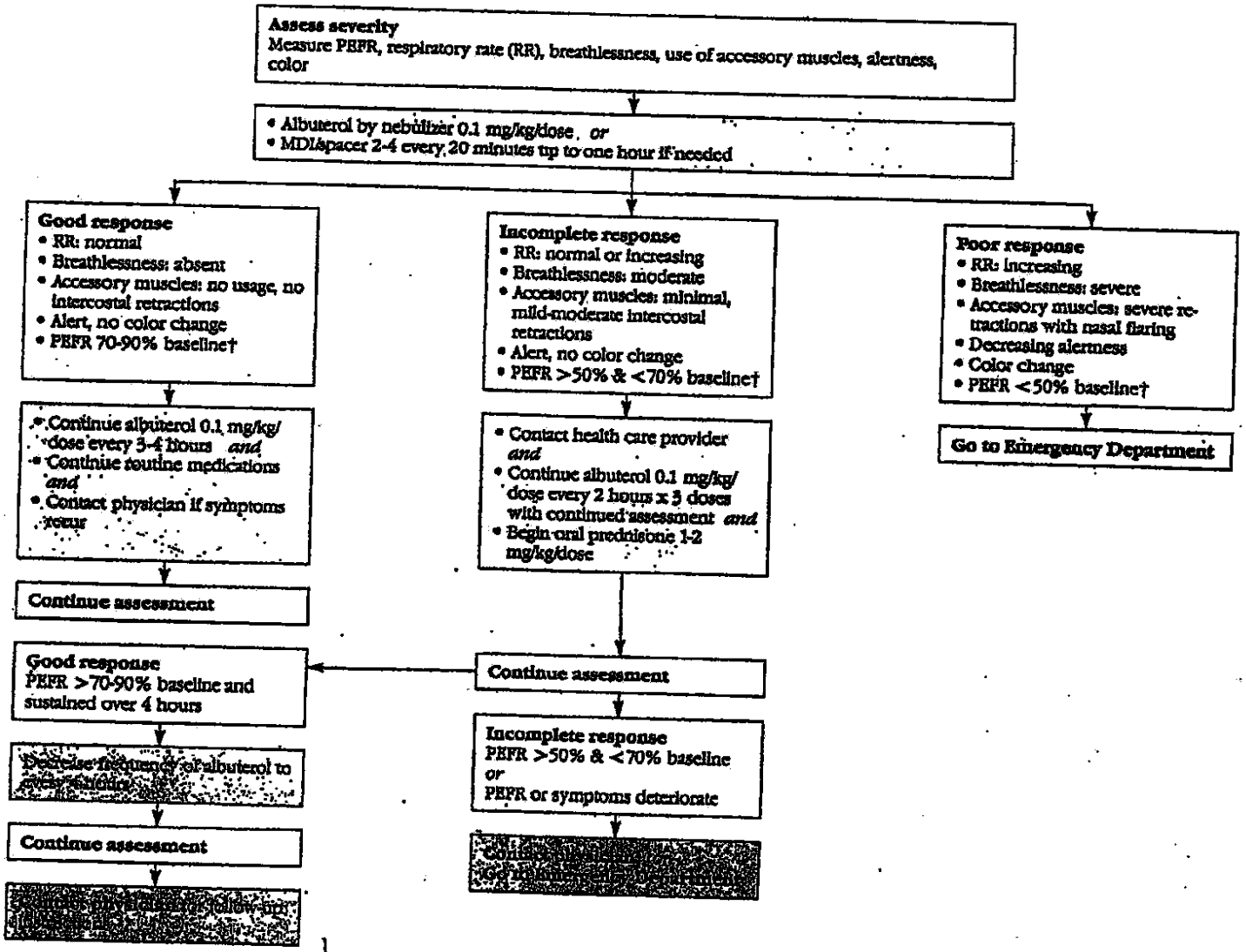
If the patient has an incomplete response to the initial therapy (PEFR >50 percent and <70 percent of predicted or personal best), the physician should be contacted for further guidance. Oral steroids usually are started at this time, and the $beta_2$-agonist is continued every 2 hours for three doses. Additional medications, such as oral theophylline, may also be recommended. It is important that the patient be continually assessed and that the physician be updated as to the patient's condition.

If there is a poor response, i.e., no improvement in symptoms or if PEFR remains low (<50 percent predicted or personal best), the patient should receive immediate medical care.

*The generic drugs named in this section are cited because studies have been made regarding using higher dosages in acute exacerbations of asthma in children.

Acute Exacerbations of Asthma in Children

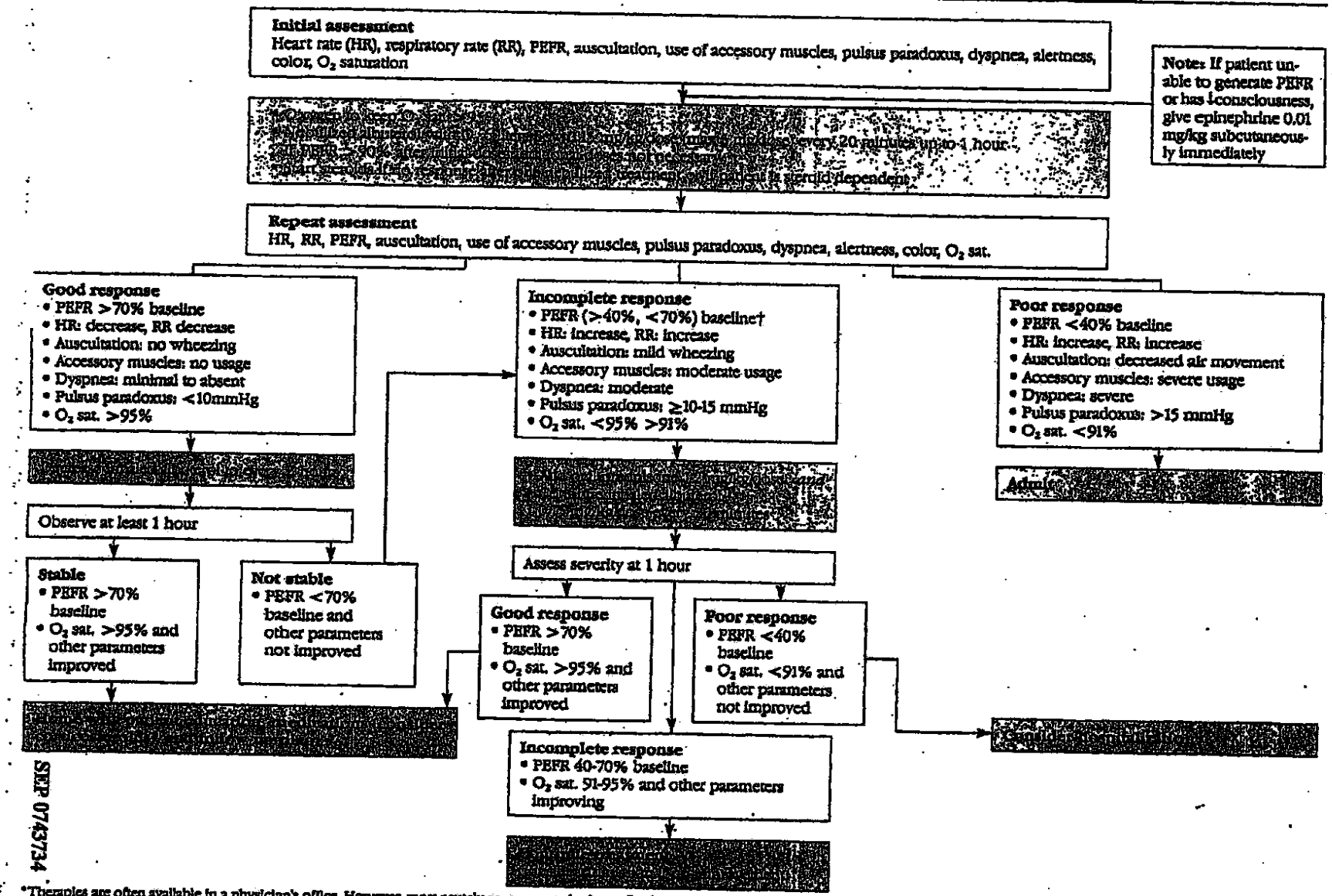
Home Management



†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best.

Acute Exacerbations of A[illegible]ma in Children

*Emergency Department Management**



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*Therapies are often available in a physician's office. However, most acutely severe exacerbations of asthma require a complete course of therapy in an Emergency Department.

†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or patient's personal best.

Physician's Office or Emergency Department Management

The discussion in this section accompanies Chart 12.

Many pediatricians and family physicians may want to treat an acute exacerbation of asthma in their office. They should have an air compressor to nebulize medications, a PEFR meter or spirometer to objectively monitor obstruction, and oxygen. If the patient fails to improve with nebulized beta$_2$-agonists given every 20 minutes for 1 hour in the office setting (PEFR >70 percent predicted or personal best), the patient should be transferred to an emergency department or hospitalized for further treatment and monitoring.

The child with an acute asthma exacerbation presenting in the physician's office and/or an emergency department should be assessed clinically as to the severity of the asthma by general activity level of the child; response to his or her environment, color, pulse rate, degree of pulsus paradoxus; use of accessory muscles; and airflow obstruction determined by auscultation. In addition, PEFR measurement should be determined in any child over 5 years of age, and continuous measurement of oxygenation with a pulse oximeter should be performed.

Initial treatment should be with a selective beta$_2$-agonist (albuterol).[42] Although other less selective beta$_2$-agonists (metaproterenol, Bronkosol) are available in nebulized form, their safety in frequently administered high doses has not been established. Albuterol can be delivered by nebulizer, preferably with oxygen. Nebulized treatments should be given every 20 minutes for 1 hour, and the patient should be continually assessed. If albuterol is not available, an injectable solution of terbutaline may be used in a nebulizer (0.3 mg/kg up to 5 mg of 1mg/1mL injectable solution undiluted every 20 minutes until improvement, then every 1-2 hours as needed; or may administer continuously at 2-4 mg/hour). This use of terbutaline is not generally recommended because it offers no advantage over albuterol, which is available as a nebulizer solution. An injectable solution of terbutaline is not FDA approved for the nebulizer.

There is no evidence that theophylline adds to the bronchodilation achieved with beta$_2$-agonists in the first 4 hours in the emergency department.[43]

If the patient has a good response to the initial treatment (PEFR <70 percent predicted or personal best), the beta$_2$-agonist treatment may be decreased to every 2 hours; the patient should be observed for at least 1 hour. If after that time the patient is stable, he or she may be discharged to home with education, medication, and a followup plan, as discussed in the second section of this chapter.

If the patient does not improve after the initial 1 hour of beta$_2$-agonist treatment (PEFR <70 percent predicted or personal best), then oral or intravenous (I.V.) steroids should be administered,[44-46] and nebulized beta$_2$-agonist treatments should be given every 20 minutes for 2 hours. The patient's status should be continually assessed, and a decision should be made in 2 hours to determine whether the patient's treatment can be continued in the emergency department, if hospitalization is necessary, or if discharge to home is possible. If improved, a patient should be observed in the emergency department for at least 1 hour to assure maintenance of improvement.

Hospital Management

The discussion in this section accompanies Chart 13.

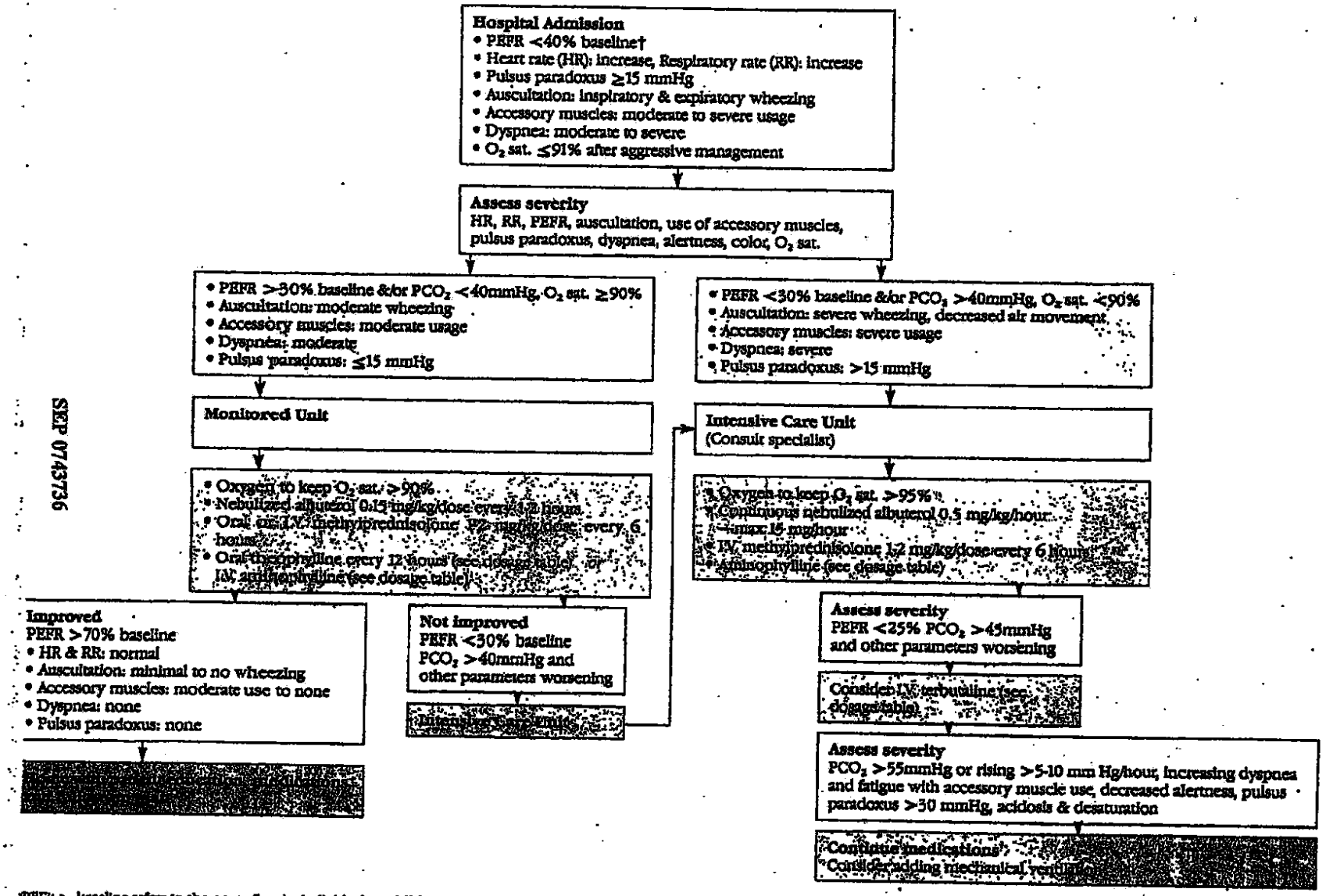
The severity of the illness should be reassessed upon admission to the hospital from the hospital emergency department or an outlying emergency department. In addition to clinical parameters and PEFR, assessment may include an arterial blood gas measurement. It must be decided whether the patient requires intensive therapy and close monitoring in an intensive care unit or intermediate care unit or if the patient is more stable and can be managed on a general monitored hospital ward. If the patient is stable enough for a general ward (PEFR >30 percent predicted or personal best, PCO_2 <40 mm Hg, O_2 saturation ≥90 percent), he or she should be treated initially with nebulized beta$_2$-agonists (albuterol) every 1-2 hours, oral or intravenous steroids every 6 hours, and oral sustained release theophylline every 12 hours or intravenous aminophylline.[17,19] In addition, the patient should be monitored closely for signs of increasing severity or improvement, which can be accomplished with PEFR monitoring in a child older than 5 years of age. If the patient improves during the next 24-48 hours, he or she may be discharged to home with education and a continued management plan. If the patient's condition deteriorates (PEFR <30 percent predicted or personal best and rising PCO_2), he or she should be transferred to an intensive care unit and be continuously assessed.

Intensive care unit management requires the help of a specialist and includes frequent blood gas assessment (usually through an arterial line), continuous pulse oximetry, and frequent PEFR monitoring. The patient admitted to the intensive care unit should be on oxygen and treated with continuous nebulized albuterol,[20-22] intravenous steroids[44-46] every 6

Chart 13

Acute Exacerbations of Asthma in Children

Hospital Management



†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best.

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hours, and intravenous aminophylline given by continuous infusion (see Figure 8-5).[7,19]

The addition of anticholinergic medications may be considered at this time by the specialist.[25,29] Nebulized ipratropium bromide has shown to be the most effective anticholinergic; however, it is not currently available in the United States in this form.

If the patient does not improve (PEFR <25 percent, PCO_2 >45 mm Hg) and other parameters are worsening, intravenous terbutaline[30,35] may be added with close monitoring. Intravenous isoproterenol is not recommended because its beta effect causes significant tachycardia and toxicity.[36] An arterial line should be placed for continuous blood pressure, heart rate, and blood gas monitoring. If a trial of intravenous terbutaline does not result in an improvement and the patient is having progressive increase in fatigue, the patient should be mechanically ventilated while continued on all medications.[37,38] Ventilation of an asthma patient is difficult and always requires the assistance of a qualified specialist.

When the patient improves, preparation for discharge follows the same guidelines presented for adults in the second section of this chapter. It is emphasized that the discharge plan will include a medication plan (usually including a short course of oral corticosteroids), patient education (including consideration of home PEFR monitoring for patients over 5 years of age), and a plan for followup with a clinician.

Special Considerations for Management of Exacerbations of Asthma in Infants

Asthma can occur in infants who are only a few weeks old. The condition can be particularly severe and difficult to monitor. More than 50 percent of children with asthma experience onset during the first 2 years of life, with at least 10 percent in the first year. Understanding the differences in lung anatomy and physiology between infants and older children may help in the management of asthma in infants.

Several differences in lung anatomy and physiology in infants place them at greater risk for respiratory failure. These include:

- Increased peripheral airway resistance.
- Deficient collateral channels of ventilation.
- Airway smooth muscle that extends in a spiral manner further into the peripheral airways.
- Decreased elastic recoil pressure.
- Mechanically disadvantaged diaphragm.

Etiology

Viral infections, particularly respiratory syncytial virus, are the most common etiology of acute asthma in children under 6 months. The pathology is frequently in the small airways or bronchioles leading to edema, air trapping and hyperinflation, atelectasis, increased respiratory rate, and wheezing. This sequence of changes can rapidly progress to respiratory failure.

Monitoring

Because of the infant's physiology, acute asthma can rapidly progress to respiratory failure. Close monitoring, therefore, is extremely important. In addition most children less than 5 years of age cannot perform PEFR measurements, so other parameters must be assessed. These parameters have not been quantitated or systematically studied, so they serve only as a general guide.

Subjective measurements that can be used in monitoring asthma in infants include:

- **General overall alertness and responsiveness to the environment.** As infants become sicker, they may not recognize or interact appropriately with their parents and familiar objects.
- **Ability to feed or suckle.** Increasing respiratory distress is indicated when an infant stops suckling or feeding.
- **Chest retractions.** Because of the compliant chest, these are often a sign of moderate airway obstruction.
- **Chest hyperinflation.** This can be seen visually or as flattened diaphragms on chest x-ray and is an indication of moderate airway obstruction.
- **Color change.** Any evidence of cyanosis is a manifestation of severe asthma.
- **Quality of infant's cry.** As the forced expiratory volume diminishes with increasing severity, the infant's cry becomes softer and shorter.

Objective measurements can be used in monitoring asthma in infants:

- **Respiratory rate.** The respiratory rate in an awake infant can vary widely, but in a sleeping infant, it is an excellent indicator of obstruction. An increase of up to 50 percent above the mean indicates moderate obstruction; more than 50 percent above the usual rate indicates severe obstruction. Figure 8-4 shows respiratory rates of normal children, sleeping and awake.

Figure 8.5
Dosages of Drugs in Acute Exacerbations of Asthma in Children

Drug	Available Form	Dosage	Comment
Inhaled Beta$_2$-Agonist			
Albuterol			
Metered-dose inhaler	90 μg/puff	2 inhalations every 5 minutes for total of 12 puffs, with monitoring of PEFR or FEV$_1$ to document response	If not improved, switch to nebulizer. If improved, decrease to 4 puffs every hour.
Nebulizer solution	0.5% (5 mg/mL)	0.1-0.15 mg/kg/dose up to 5 mg every 20 minutes for 1-2 hours (minimum dose 1.25 mg/dose)[a]	If improved, decrease to 1-2 hours. If not improved, use by continuous inhalation.
		0.5 mg/kg/hr by continuous nebulization[a,b] (maximum 15 mg/hour)	
Metaproterenol			
Metered-dose inhaler	650 μg/puff	2 inhalations	Frequent high-dose administration has not been evaluated. Metaproterenol is not interchangeable with beta$_2$-agonists albuterol and terbutaline.
Nebulizer solution	5% (50 mg/mL)	0.1-0.3 cc (5-15 mg). Do not exceed 15 mg.	
	0.6% unit dose vial of 2.5 mL (15 mg)	As above 5-15 mg. Do not exceed 15 mg.	
Terbutaline			
Metered-dose inhaler	200 μg/puff	2 inhalations every 5 minutes for a total of 12 puffs	
Injectable solution used in nebulizer	0.1% (1 mg/1 mL) solution in 0.9% NaCl solution for injection		Not recommended because not available as nebulizer solution. Offers no advantage over albuterol, which is available as nebulizer solution.
	Not FDA approved for inhalation.		
Systemic Beta-Agonist			
Epinephrine HCl	1:1000 (1 mg/mL)	0.01 mg/kg up to 0.3 mg subcutaneously every 20 minutes for 3 doses.	Inhaled beta$_2$-agonist preferred.
Terbutaline	(0.1%) 1 mg/mL solution for injection in 0.9% NaCl.	Subcutaneous 0.01 mg/kg up to 0.3 mg every 2-6 hours as needed. Intravenous 10 μg/kg over 10 minutes loading dose. Maintenance: 0.4 μg/kg/min. Increase as necessary by 0.2 μg/kg/min and expect to use 3-6 μg/kg/ min.[a]	Inhaled beta$_2$-agonist preferred.

Figure 8.5
Dosages of Drugs in Acute Exacerbations of Asthma in Children (continued)

Drug	Available Form	Dosage	Comment
Methylxanthines			
Theophylline	Aminophylline (80% anhydrous theophylline)	Loading dose:* If theophylline concentration known: every 1 mg/kg aminophylline will give 2 μg/mL increase in concentration.	
		Loading dose:* If theophylline concentration is unknown: —No previous theophylline: 6 mg/kg aminophylline —Previous theophylline: 3 mg/kg aminophylline	
		Constant infusion Rates:* Infusion rates to obtain a mean steady-state concentration of 15 μg/mL:	
		Age 1-6 months 6 mo-1 year 1-9 years 10-16 years	0.5 mg/kg/hr aminophylline 1.0 mg/kg/hr aminophylline 1.5 mg/kg/hr aminophylline 1.2 mg/kg/hr aminophylline
Corticosteroids			
Outpatients:	Oral prednisone, prednisolone, or methylprednisolone	1-2 mg/kg/day in single or divided doses.	Reassess at 3 days as only a short burst may be needed. No need to taper dose.
Emergency Department or hospitalized patients:	Methylprednisolone I.V. or P.O.	1-2 mg/kg/dose every 6 hrs for 24 hrs then 1-2 mg/kg/day in divided doses q 8-12 hours.	Length depends on response. May only need a few days.

*Check serum concentration at approximately 1, 12, and 24 hours after starting the infusion.

Oxygen saturation. Because of the ventilation/perfusion abnormalities in infants, they will become hypoxemic earlier than adults. Thus, oxygen saturation measurements should be performed on all infants by pulse oximetry and should be greater than 93 percent. Decreased oxygen saturation is often an early sign of moderate to severe airway obstruction.

Arterial or capillary blood gases. These should be performed in all infants with 0_2 saturation <90 percent. The PCO_2 is the best measurement of ventilation in an infant. A capillary blood gas with a PCO_2 of >35 mm Hg should be repeated at frequent intervals, or infants should have continuous $TcCO_2$ measurement. Infants with moderate-to-severe airway obstruction should have capillary or arterial blood gases measured at least every 6 hours. A patient with a PCO_2 > 50 mm Hg or rising 5-10 mm Hg/hr or more is a candidate for mechanical ventilation and should be observed carefully for increasing fatigue.

Treatment

Infants with acute asthma are treated the same as older children and adults in the emergency department or hospital.

Beta$_2$-agonists by nebulization are the bronchodilator of choice. Reports of poor response to these agents may be caused by too low a dose or poor delivery. Albuterol should be administered by mask with a minimum dose of 1.25 mg and treatment should be repeated as in the flow charts and dose table (Figure 8-5) for older children.

Corticosteroids are particularly important in infants because of the airway edema that occurs. These agents should be given very early in the course of acute asthma and should be started if the infant fails to completely respond to two albuterol inhalations.

Theophylline. Metabolism of theophylline is considerably reduced in the first 6 months of life and increases later in childhood. Doses should be adjusted appropriately.

Anticholinergics. Studies have shown that nebulized ipratroprium bromide is effective in infants; however, the drug is not yet available in the United States as a nebulizer solution.

Special Cases

Bronchopulmonary Dysplasia

Some infants born prematurely develop chronic lung disease and have repeated bouts of severe wheezing. These infants benefit from bronchodilators and anti-inflammatory medications.

Cystic Fibrosis

Infants with cystic fibrosis may also have acute exacerbations of wheezing hyperinflation resulting from struction of small airways. This group of patients may benefit from bronchodilators and anti-inflammatory medications.

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9
Exercise-Induced Asthma

Most people with asthma have airway hyperirritability that leads to exercise-induced asthma (EIA). Therefore, this condition should be anticipated in all asthma patients. For some people with asthma, exercise is the only trigger. Approximately 40 percent of children who have allergic rhinitis, but who do not have clinical asthma, have EIA.[1] This situation is probably true for the same percentage of adults.

Untreated EIA can limit and disrupt normal life. Although individual episodes of EIA are short lived, their severity and impact can be striking. As a result, in the long term, people with untreated EIA often limit their activities unnecessarily.

Chart 14 accompanies this chapter's discussion.

Pathophysiology

Exercise-induced asthma refers to airway narrowing that occurs minutes after the onset of vigorous activity. It generally reaches its peak about 5-10 minutes after cessation of activity and usually resolves in another 20-30 minutes. Figure 9-1 shows the typical time course and lung function changes of a person with EIA who is challenged with an exercise period.[2,3]

The existence of a late phase of EIA, occurring 4-12 hours after the initial exacerbation, is now being assessed.[4] This late phase, if it does exist, is uncommon and not severe, unlike the late phase of allergen-induced asthma, which can be serious.

For some patients who engage in continuous, repetitive exercise periods, EIA diminishes or is completely abated during a refractory period that usually lasts 2 hours after an exercise challenge. During this period, EIA is significantly reduced from its initial level.[2]

Although asthma, in general, is characterized by smooth muscle constriction and airway inflammation, exercise-induced asthma is due mainly to smooth muscle constriction. Therefore, some investigators prefer the term "exercise-induced bronchospasm" (EIB) to "exercise-induced asthma" (EIA). Both terms are used.

While some debate remains,[5] it is generally established that EIA results from loss of heat or water, or both, from the lung during exercise. This results from hyperventilation of air that is cooler and dryer than that of the respiratory tree.[6] The chain of events that ties heat and water loss to airway narrowing has not yet been clarified. It has been suggested that heat and water loss leads to changes in airway osmolarity that cause constriction in the smooth muscles.

Most asthma patients should be able to participate in any activity they choose without experiencing asthma symptoms.

Diagnosing EIA

Taking a History

A history of cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercise suggests EIA.

Conducting an Exercise Challenge

When there is doubt, an exercise challenge can establish a diagnosis of EIA. In an exercise challenge, the patient exercises at a level of ventilation high enough to produce the intra-airway thermal events that evoke obstruction. This situation can usually be achieved through exercise for 4-8 minutes that achieves 50 percent or more of the patient's maximum predicted oxygen consumption.

An exercise challenge can be formal or informal. If a patient complains of problems with exercise, an adequate challenge would consist of having the patient undertake whatever task has caused the problem. In the formal laboratory setting, challenge is often done with treadmill exercise capable of raising the patient's heart rate to that which produces 80-90 percent of oxygen utilization by the heart for a period of 6-8 minutes.[7] Pulmonary function measurements, e.g., PEFR and FEV_1, are determined before and after exercise and at 5-minute intervals for 20-30 minutes. Although a drop in PEFR or FEV_1 of greater than 12 percent is compatible with EIA,[8] using a decrease of 15 percent may be more acceptable; this is because it avoids the possibility of confusing variability of spirometry technique with a true drop in pulmonary function. The best of three expiratory maneuvers is taken at each time period.

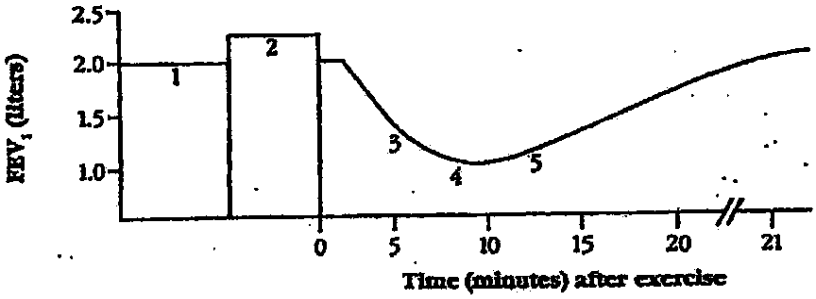
Alternatively, the clinician can have the patient run outdoors for 4-8 minutes at a brisk pace. PEFR can be monitored after this challenge. This free run challenge can actually be more asthmogenic than the treadmill because air coolness and dryness will enhance the asthmatic response.

For middle-age and elderly people, it is important to conduct the exercise challenge in a facility with the capability to monitor heart rate and rhythm as part of the challenge.

Managing EIA

The goal of treating EIA is to enable patients to participate in any activity they choose without experiencing asthma symptoms. Many Olympic athletes have asthma: 67 athletes at the 1984 Olympic games had asthma; many won medals.[9] Athletic conditioning can improve muscle and

Figure 9-1
Course of Exercise-Induced Asthma



1. Baseline lung function.
2. Exercise.
3. Striking drop in FEV_1 beginning a few minutes after cessation of exercise.
4. Decline reaches its lowest point 5 to 10 minutes after cessation of exercise.
5. By the end of 20 minutes, FEV_1 has largely improved.

...ercising efficiency and thereby decrease one's level of ventilation, but it does not modify EIA for a given level of ventilation.[10]

Inhaled beta$_2$-agonists, used prior to exercise, will abate EIA in more than 80 percent of subjects.[4] Children ages 4-5 years may be able to use a metered-dose inhaler if a spacer device is provided. These may be taken from less than 5 to 60 minutes prior to exercise and are helpful for up to several hours. However, because effectiveness does decrease with time, it is preferable to take medication just before exercise, if possible. Cromolyn sodium (2 puffs) before exercise is another acceptable pretreatment. The small percentage of patients who still encounter difficulty are helped by an increased dosage of beta$_2$-agonist or use of both beta$_2$-agonist and cromolyn. Patients who experience a refractory period during continuous exercise may benefit from a warmup period before exercise and may not need repeated medications during periods of continuous exercise.

Beta$_2$-agonist with or without cromolyn for younger children who use home nebulizers may be administered prior to exercise and timed like metered-dose inhalers. Examples are albuterol (0.1-0.15 mg/kg in 2 cc of saline) or 1 ampule cromolyn; or metaproterenol (0.25-0.50 mg/kg in 2 cc of saline) or 1 ampule cromolyn (20 mg).

There are alternative forms of bronchodilators for younger children who cannot use a metered-dose inhaler or who do not have a home nebulizer. For young children, oral liquid bronchodilators (albuterol 5 cc [2 mg], metaproterenol 5 cc [10 mg]) given 30 minutes before exercise may be helpful. Rapidly absorbed theophylline may be used but requires 1 hour to reach peak levels, may cause gastrointestinal upset or headache when used intermittently, and is less effective than inhaled beta$_2$-agonist.

Medications that are approved by the U.S. Olympic Committee (USOC) for use in competition include:

Beta$_2$-agonists (aerosol or inhalant form only).
—Albuterol.
—Bitolterol.
—Terbutaline.

Cromolyn sodium.

Theophylline (aminophylline).

Inhaled corticosteroids. (Written notification of such use is given in advance by the team physician to the International Olympic Committee Medical Commission or USOC Drug Control Program.[12])

Teachers and coaches should be notified that a child has EIA. This condition should not limit either participation or success in activities but may require the use of inhaled medication before activity and later if needed.

Patients should be monitored regularly to ensure that they do not have symptoms of asthma or reductions in PEFR between exercise periods. Although exercise can be the only trigger for some people with asthma, symptoms with exercise are often markers of an underlying asthma management problem that requires an evaluation of the overall treatment plan.

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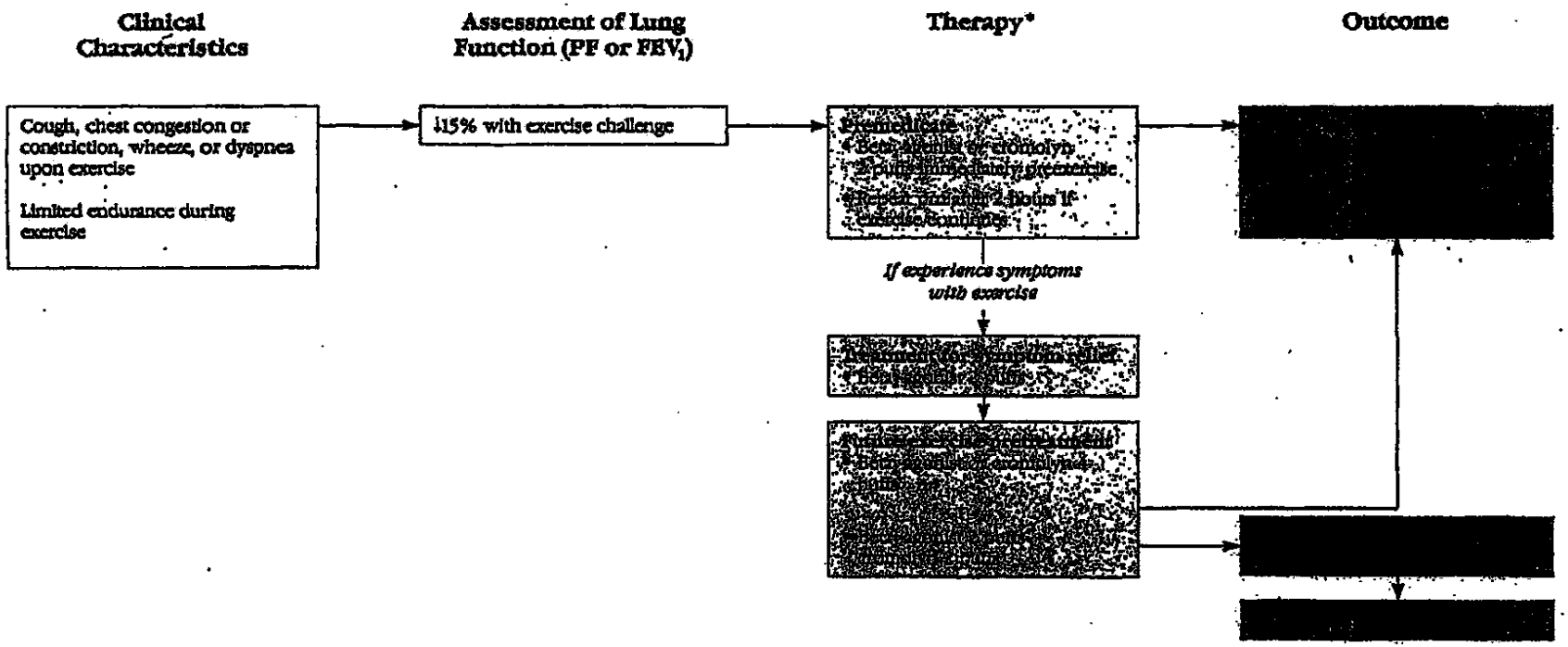
Exercise-Induced Asthma



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*All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.

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10
Special Considerations

Particular events in an asthma patient's life may necessitate adjustment of the asthma management guidelines. This chapter outlines special considerations to be made for pregnancy, surgery, older patients with asthma, and occupationally related asthma.

Furthermore, there are medical conditions that can aggravate asthma or be aggravated by asthma, or both. Special attention needs to be paid to rhinitis, sinusitis, and nasal polyps, aspirin sensitivity, sulfite sensitivity, tartrazine sensitivity, and gastroesophageal reflux. This chapter, therefore, also discusses the relationship of these conditions to asthma management.

Pregnancy and Asthma

This section discusses special considerations in managing asthma during pregnancy, including the importance of ensuring an adequate oxygen supply to the fetus while avoiding, as much as possible, drugs that pose a risk.

Pathophysiology

Effect of Pregnancy on the Course of Asthma

Retrospective studies suggest that, in approximately one-third of women, asthma becomes worse during pregnancy; in one-third, it becomes better; and in one-third, it remains unchanged. In women whose asthma becomes worse during pregnancy, peak severity occurs at 29-36 weeks of gestation. Asthma becomes less severe during the last 4 weeks of pregnancy. Wheezing during labor and delivery is uncommon, occurring in only 10 percent of women and usually responding to inhaled bronchodilator therapy.

The change in the severity of asthma during pregnancy is sometimes dramatic and tends to be consistent in subsequent pregnancies. Most women return to a prepregnancy level of severity by 3 months postpartum.[1]

Effect of Asthma on the Outcome of Pregnancy

Poorly controlled asthma has been shown to have an adverse effect on the fetus, resulting in increased perinatal mortality, increased prematurity, and low birth weight.[2] For this reason, the use of drugs to obtain optimal control of asthma is justified even when their safety in pregnancy has not been unequivocally proven.

Pregnant, surgical, or elderly patients, or those patients with medical conditions that may aggravate asthma can still expect to reach the goals for asthma therapy if special adjustments are made to the asthma management guidelines.

Effect of Drugs on Fetal Development

Because rhinitis is a common co-condition in asthma, drugs frequently prescribed for rhinitis are included in this discussion.

Between fertilization and implantation, the embryo is resistant to all environmental agents. However, by week 5 of gestation, placental transportation of low-molecular-weight substances from mother to fetus is established. The most critical period for the fetus is during organogenesis, which is largely completed between weeks 8 and 10 of gestation. Thereafter, drugs cannot cause gross abnormalities but can affect fetal growth and the functioning of organs and tissues.

For most drugs used to treat asthma, clear documentation of teratogenic effects is lacking. However, it should be stressed that these drugs have not yet been proven safe. Nevertheless, their use is preferable to uncontrolled asthma with its demonstrated risk of placental hypoxemia.

The principal information on the safety of drugs used during pregnancy is derived from the Collaborative Perinatal Project Study of 1959-1965. A total of 50,282 maternal-fetal pairs were followed prospectively for drug use during the first trimester of pregnancy. An expected frequency of congenital malformations of 1.00 was established, and relative risks were calculated for the drugs used by the women. Figure 10-1 shows the results for a number of drugs relevant to the treatment of asthma and rhinitis.

Some of the most popular and effective drugs for the treatment of asthma and rhinitis were not available when the Collaborative Study was conducted. Subsequent limited studies have appeared suggesting that cromolyn sodium, inhaled beclomethasone dipropionate, and inhaled beta-adrenergic agonists[3] are not associated with an increased incidence of fetal anomalies. Thus, there is little to suggest an increased risk with the standard asthma and rhinitis medications, with the exception of the alpha-adrenergic compounds (phenylpropanolamine, phenylephrine), brompheniramine, and epinephrine, which, in addition to its beta-stimulant properties, also has some alpha-adrenergic-stimulant activity. No data are available, however, on the newer antihistamine preparations.

Effect of Drugs During Lactation

Most drugs are secreted in the mother's milk, often in concentrations that approach those in maternal serum. However, medications used for the treatment of asthma and rhinitis rarely present a problem for the infant.

■ **Theophylline.** Less than 1 percent of the dose of theophylline administered to the mother appears in breast milk, so infant doses of 0.7-2.8 mg/kg/24 hours would be expected with a mother who has therapeutic

levels. This is a dose well under that prescribed for infants for treatment of apnea.

■ **Prednisone** also passes into the milk in low concentrations; it has been estimated that a 50-mg oral dose of prednisone to the mother would result in the infant receiving less than 20 percent of its daily physiologic corticosteroid requirement.

■ **Inhaled medications** for asthma produce very low serum levels and would not result in a significant dose to the infant.

■ **Antihistamines** are excreted in the milk in small quantities, but there are no reports of significant side effects in nursing infants.

Managing Asthma During Pregnancy

Care of Chronic Asthma

While it is generally desirable to use as few medications as possible during pregnancy, it is essential to maintain sufficient lung function and blood oxygenation to ensure adequate oxygen supply to the fetus. Nonpharmacologic control is important. Therefore, control of house-dust mites, animal dander, pollen, and mold spores should be reviewed and improved. Patients should avoid irritant triggers, especially passive exposure to tobacco smoke.

The goals and general approach of drug therapy in pregnancy are the same as in chronic care for asthma. During pregnancy, however, inhaled medications are preferred. Systemic drugs should be given when inhaled medications are not sufficient to control symptoms and normalize pulmonary function.

Risk factors have been established for drug use during pregnancy.[4] However, it is to be emphasized that the greater risk to the fetus is uncontrolled asthma. As shown in Figure 10-2, most of the drugs employed for the treatment of asthma and rhinitis have been assigned to Category B (no evidence of risk in humans) or Category C (risk cannot be ruled out) either by the manufacturer[5] or by others employing similar criteria.[6]

Figure 10-1
Risk of Allergy Medications in First Trimester of Pregnancy

Drug	Number of Patients Exposed	Standardized Risk*	Significance
Corticosteroids	145	0.67	
Tripelenamine	100	0.81	
Isoproterenol	31	0.94	
Atroprine	401	1.04	
Ephedrine	373	1.07	
Chlorpheniramine	1,070	1.20	
Diphenhydramine	595	1.25	
Phenylephrine	1,249	1.31	<0.05
Theophylline	117	1.38	
Phenylpropanolamine	726	1.40	<0.01
Hydroxyzine	50	1.44	
Epinephrine	189	1.71	<0.05
Brompheniramine	65	2.34	<0.05

**Normalized risk is 1.00.*

Other classes of drugs with some possibility of risk to the fetus include:

■ **Decongestants.** Avoid all oral alpha-adrenergic agonists.

■ **Antibiotics.** Avoid tetracycline, aminoglycosides, sulfonamides, and ciprofloxacine.

■ **Vaccines.** Avoid live virus vaccine. Killed virus vaccines are acceptable.

■ **Immunotherapy.** Do not begin allergy immunotherapy. In patients already receiving immunotherapy, consider maintaining current dose.

■ **Iodides.** Avoid.

Alpha-adrenergic compounds. Avoid, for example, epinephrine, phenylpropanolamine, phenylephrine.

Treatment of Acute Exacerbations

It is particularly important to avoid fetal hypoxia. Treatment of acute episodes should include nebulized beta-agonists and oxygen. If parenteral beta-agonists are required, terbutaline is preferred over epinephrine. Parenteral corticosteroids should be instituted in all but the mildest exacerbations to improve oxygenation and prevent relapses. Theophylline levels should be monitored during pregnancy.

Figure 10-2
Risk to Fetus of Allergy and Asthma Medications During Pregnancy[16]

	Risk Factor Category According to Manufacturer's FDA Approved Product Labeling
Bronchodilator	
Albuterol	C
Metaproterenol	C
Terbutaline	B
Theophylline	C
Anti-inflammatory	
Cromolyn sodium	B
Beclomethasone dipropionate	C
Prednisone	(Not rated)
Flunisolide	C
Triamcinolone	D
Antihistamine	
Chlorpheniramine	B
Brompheniramine	C
Terfenadine	C
Astemizole	C
Triprolidine	B

Key to Risk Factor Ratings

Category

A **Controlled studies show no risk.** Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

B **No evidence of risk in humans.** Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.

C **Risk cannot be ruled out.** Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. However, potential benefits may justify the potential risk.

D **Positive evidence of risk.** Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.

X **Contraindicated in pregnancy.** Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

Treatment During Labor

No special treatment is required for most women during labor. However, for those who have received daily parenteral corticosteroids for a recent 1-week course or three separate courses in the preceding year, hydrocortisone supplementation (100 mg hydrocortisone every 8 hours) for the stress of delivery is recommended unless there is documentation of normal adrenal responsiveness.

Surgery and Asthma

Bronchial hyperresponsiveness, airflow obstruction, and mucus hypersecretion predispose asthma patients to intraoperative and postoperative respiratory complications. The general medical physician may be asked to participate in the preoperative evaluation of the asthma patient. This involves assessing the risk of anesthesia and surgery and intervening to minimize that risk. This section addresses major elements to be considered in preoperative evaluation.

Possible Complications

The following potential complications may occur at the time of surgery.

- Endotracheal intubation may trigger acute neurally mediated bronchoconstriction. (Stimulation of sensory receptors in the upper airway can lead to reflex efferent neurotransmission via the vagus nerve, resulting in bronchial smooth muscle contraction.)
- Airflow obstruction causes ventilation-perfusion mismatching and may contribute to impaired gas exchange (hypoxemia and possibly hypercapnia) during and after surgery.
- Severe airflow obstruction, along with postoperative pain, can impair the effectiveness of cough. Retained airway secretions can further impair airflow and gas exchange.
- Mucus plugging can cause atelectasis and can also predispose a patient to respiratory infection.

The likelihood of these complications depends on the severity of the patient's airway hyperresponsiveness, the degree of airflow obstruction, and the amount of excess airway secretions at the time of surgery. These variables can be assessed prior to surgery by history, physical examination, and measurement of expiratory airflow (spirometry or peak expiratory flow determination). Other factors influencing the rate of postoperative complications are the type of surgery (thoracic and upper abdominal surgery pose the greatest risks) and type of anesthesia (general anesthesia with endotracheal intubation carries the greatest risk).

Preoperative Assessment

All patients with active asthma (symptoms of disease within the past year) should undergo preoperative respiratory evaluation. Even asymptomatic asthma patients may have significant airflow obstruction and bronchial hyperresponsiveness and should be evaluated. In patients with moderate to severe disease (i.e., patients requiring daily medication), this evaluation should begin several days prior to elective surgery to provide adequate time for preoperative care. In some extreme instances, hospitalization for a day or more prior to surgery may be recommended for optimization of lung function. Unnecessary delay of elective surgery can best be avoided by early preoperative respiratory evaluation.

Certain special aspects of the asthma patient's medical history suggest a particularly heightened risk for perioperative complications:

- Frequent nocturnal awakenings from asthma (a potential indicator of increased bronchial hyperresponsiveness).
- Requirement for frequent or continuous use of systemic corticosteroids, or recent hospitalization(s) or emergency department visit(s) for asthma.
- Prior perioperative complications related to asthma.
- Large volumes of sputum production.
- Comorbid cardiovascular disease.

Spirometry or peak expiratory flow rate (PEFR) determination is an indispensable part of the preoperative assessment in the asthma patient. The forced expiratory volume (FEV_1) or PEFR serves to quantify the severity of airflow obstruction. Most useful is comparison of the measured FEV_1 or PEFR with the patient's best value for FEV_1 or PEFR, as recorded in recent weeks or months. This comparison allows calculation of the degree of improvement required to optimize the patient's lung function. If prior values are not available, the goal of achieving predicted normal lung function should be set.

Managing Surgery and Asthma

Optimize Lung Function

Asthma patients experiencing wheezing, productive cough, chest tightness, or shortness of breath should receive intensified treatment of their asthma prior to elective surgery, even if this necessitates delay of surgery. Likewise, an attempt should be made to improve lung function in patients with an FEV_1 or PEFR <80 percent of predicted or <80 percent of their recent best values. Frequently, a brief course of corticosteroids will be required to achieve this goal. The adverse effects of systemic corticosteroids on adrenal-pituitary function and surgical wound healing do not contraindicate their preoperative use.

Anesthesia

Modification of the anesthetic approach may be possible in some patients at increased perioperative risk (see above). In particular, spinal, epidural, or local anesthesia may in some cases be substituted for general anesthesia, and postoperative pain control may utilize epidural analgesia rather than parenteral narcotic analgesics.

Medications

Even in the asymptomatic or minimally symptomatic patient, it is useful to administer an inhaled $beta_2$-agonist bronchodilator (by metered-dose inhaler, dry powder inhaler, or hand-held nebulizer) immediately prior to surgery. This can be safely achieved even in patients receiving nothing by mouth and serves to minimize the risk of bronchoconstriction induced at the time of endotracheal intubation.

Patients receiving daily antiasthmatic medications should generally be maintained on these medications. Intravenous aminophylline can be used to maintain therapeutic blood levels of theophylline in patients who regularly take this medication but for surgery are not permitted to take anything by mouth (N.P.O.). The usual maintenance dose of intravenous aminophylline is 0.6 mg/kg/hr by continuous infusion; the rate is increased or decreased by factors that modify theophylline clearance by the liver. If a therapeutic blood level was achieved with the oral dosing regimen of theophylline, the aminophylline infusion rate can be calculated as follows: Aminophylline infusion rate (mg/hr) = total daily theophylline dose (mg) × 1.25/24 hr.

Inhaled bronchodilators can be maintained intraoperatively even among patients receiving general anesthesia and mechanically assisted ventilation. Adaptors fitted in the circuit of the anesthesia tubing permit inline delivery of $beta_2$-agonist bronchodilators either from metered-dose inhalers or hand-held nebulizers. During the immediate perioperative period, administration of inhaled corticosteroids and cromolyn is generally not necessary and can be omitted.

Patients who have been taking systemic corticosteroids regularly (whether daily or every other day) or in frequent brief courses can be expected to have a depressed adrenal-pituitary response to stress, including the stress of surgery. They are at risk for relative adrenal insufficiency during and after surgery. To prevent this complication, any patient who has received systemic corticosteroids for more than 2 weeks within the last 6 months (or more than two courses of systemic corticosteroids within the last 12 months) should be given intraoperative and postoperative steroid supplementation. Patients who have been taking high-dose inhaled corticosteroids—more than the conventional recommended doses of inhaled beclomethasone, triamcinolone, or flunisolide—should also be considered at risk for relative adrenal-pituitary suppression and should be given perioperative steroid replacement therapy.

The usual dose of corticosteroids for replacement therapy during periods of stress is 300 mg of hydrocortisone per day. A typical regimen for the day of surgery is:

- Hydrocortisone, 100 mg by intravenous bolus preoperatively on the morning of surgery.
- Hydrocortisone, 100 mg added to the intraoperative intravenous fluids.
- Hydrocortisone, 100 mg by intravenous bolus postoperatively.

The systemic corticosteroids are then tapered over the next few days; the rapidity of the tapering depends on the magnitude of the surgery and the nature of the patient's postoperative course.

Clearing Airway Secretions

Clearance of increased airway secretions may be an important aspect of postoperative care. Chest physiotherapy, adequate analgesia, and avoidance of dehydration are helpful in the prevention of postoperative mucus plugging and pulmonary atelectasis.

Older Patients with Asthma

Various studies indicate that the increase in asthma mortality throughout the world is more marked in older (more than 55 years of age) patients with asthma (see also Chapter 3, Asthma Mortality). Several possible explanations have been considered.

First, because of diagnostic difficulties, the precise cause of severe airflow obstruction is sometimes difficult to identify. Some cases of asthma diagnosed in older adults may actually be a combination of asthma and chronic obstructive pulmonary disease or of asthma and congestive heart failure.

Second, when an older adult with asthma has coexisting disease, asthma exacerbations can cause additional problems. For example, in a patient with both asthma and ischemic heart disease, an acute exacerbation of asthma associated with hypoxemia could result in decreased myocardial oxygenation followed by myocardial muscle damage or rhythm disturbances.

Third, medication employed for other diseases may aggravate asthma. Arthritis often coexists with asthma. Aspirin and other nonsteroidal anti-inflammatory agents frequently used to treat arthritis may cause sudden and severe asthma exacerbation in some individuals (see Section F in this chapter). Beta blockers found in some eye drops can aggravate asthma. Nonselective beta blockers, commonly used to treat hypertension, frequently trigger asthma exacerbations. Because hypertension commonly coexists with asthma, it is very important to be aware of the use of these medications. Furthermore, theophylline and the alpha-adrenergic stimulant properties of epinephrine have the potential to exacerbate underlying heart conditions.

Treatment Considerations

Treatment of asthma and of acute asthma exacerbations should follow the recommended guidelines for adults, with the following special considerations:

Evaluate all asthma patients over 55 years old for coexisting disturbances and the possibility of complications. Particular attention should be given to the monitoring of hypoxemia in older asthma patients with heart disease, taking precautions in the use of drugs likely to induce cardiac arrythmias. Any older person with asthma should be followed carefully because of the possibility of undocumented heart disease.

Consider altering medications. Theophylline may increase the risk of urinary retention in older men with prostatism. There have been a few reports of similar effects with antihistamines. When theophylline appears to create urinary problems, consider reducing the dose or substituting, for example, ipratropium bromide or inhaled anti-inflammatory agents such as inhaled corticosteroids or cromolyn.

Monitor patients on chronic systemic corticosteroid therapy by:

- —Obtaining hematocrit and blood sugar periodically to rule out hyperglycemia, hypokalemia, and gastrointestinal bleeding.
- —Conducting an eye examination annually to rule out cataracts or glaucoma.
- —Evaluating possible alterations in calcium homeostasis in patients for whom there is a concern about bone loss. (Appropriate treatment to prevent bone loss, which may require consultation with an endocrinologist may be initiated.)

Use oxygen therapy with caution. Oxygen is often required during an acute asthma exacerbation. Because of the difficulty in separating asthma and chronic obstructive lung disease in older adults, much more caution is required in the use of oxygen; CO_2 retention and alveolar hypoventilation are more likely in this population. Therefore, low-flow oxygen and blood gas monitoring during the acute exacerbation are important.

Assess patients for depression and other serious psychiatric illness. Depression has been identified as a risk factor for fatality-prone asthma. Older adults are more likely to experience family loss and disruption, difficult adjustments to retirement, and other kinds of psychosocial problems. Assessment of older patients for the presence of these conditions will help identify the possibility of increased risk and thus the need for special monitoring and/or referral.

Consider impairments. Certain impairments common among older patients may interfere with treatment.

—Arthritis patients with asthma may require special devices such as vent-ease or spacers to assist in actuating a metered-dose inhaler. Nebulizers might be prescribed as an alternative.

—Patients with visual impairment may be unable to read the numbers on their peak flow meters (in which case color-coded marks on the meter may help). These patients may also need special easy-to-read dispensers for liquid medications. Patient education materials that are printed in large type and use visual aids are recommended.

—Patients with memory difficulties may not be able to adhere to medical regimens that require several drugs and alternating schedules. The use of combination medications and simplified regimens written in large print improves adherence.

—Patients with hearing loss may not tell the health care provider that they have not heard or understood the instructions. Asking the patients to state the information and/or instructions in their own words will help ensure understanding.

Occupational Asthma

An estimated 2 percent of all asthma may be of occupational origin. Few large surveys are available, but the incidence of occupational asthma ranges from approximately 4-10 percent among persons exposed to laboratory animals to 44 percent among workers in small bakeries. More than 200 sensitizing agents have been identified in the workplace. Figure 10-3 lists some agents known to cause asthma in selected occupations.

Diagnosing Occupational Asthma

Occupational asthma can be diagnosed when:

- A worker has respiratory symptoms and evidence of reversible airway obstruction.
- There is a relationship between a specific sensitizing agent encountered in the workplace and the occurrence of respiratory symptoms.

Taking a History

A thorough patient history must be taken to distinguish between (1) pre-existing asthma that is exacerbated by exertion or nonspecific irritant exposures in the workplace and (2) asthma that is caused solely by exposure to a specific sensitizing substance at the worksite. The latter is considered occupational asthma. In certain states, occupational asthma is a reportable disease.

Identifying Symptoms

There is often a latent period of weeks or, in some cases, years between first exposure and the onset of symptoms. Once symptoms develop, they tend to become progressively more severe with continued exposure. Symptoms include the following:

- **Rhinitis or ocular irritation** is usually the first symptom experienced. It may occur within minutes of exposure and may disappear soon after the worker leaves the workplace.
- **Pulmonary symptoms** may first be a cough rather than wheezing and may first occur in the evening after work or during the night.
- **More typical asthma symptoms** (cough and wheeze, tight chest, dyspnea) appear with continued exposure and begin to occur in closer proximity to the work exposure.
- **Symptoms clearing over weekends** may be one of the first clues to a possible occupational etiology of the patient's asthma. However, in some instances, improvement over the weekend is negligible, and the symptoms subside only after 1-2 weeks away from work.

Workers with occupational asthma who continue to be exposed are at increased risk for persistent asthma. Further, symptoms may continue for years among as many as two-thirds or more of patients with occupational asthma, even after their workplace exposure stops.

Identifying the Source of Occupational Asthma

Several methods can help identify the agent responsible for the worker's asthma:

- **Patient history** questions about which substances are used in the patient's workplace may reveal occupational exposure to a known sensitizer (see Figure 10-3).

Figure 10-3
Agents Causing Asthma in Selected Occupations

Occupation or Occupational Field	Agent
laboratory animal workers, veterinarians	dander and urine proteins
food processing	shellfish, egg proteins, pancreatic enzymes, papain, amylase
dairy farmers	storage mites
poultry farmers	poultry mites, droppings and feathers
granary workers	storage mites, aspergillus, indoor ragweed, and grass pollen
research workers	locusts
fish food manufacturing	midges
detergent manufacturing	*Bacillus subtilis* enzymes
silk workers	silk-worm moths and larvas
	Plant Proteins:
bakers	flour
food processing	coffee bean dust, meat tenderizer (papain), tea
farmers	soy bean dust
shipping workers	grain dust (molds, insects, grain)
laxative manufacturing	ispaghula
sawmill workers, carpenters	wood dust (western red cedar, oak, mahogany, zebrawood, redwood, Lebanon cedar, African maple, eastern white cedar)
electric soldering	colophony (pine resin)
cotton textile workers	cotton dust
nurses	psyllium
	Inorganic Chemicals:
refining	platinum salts
plating	nickel salts
diamond polishing	cobalt salts
stainless steel welding	chromium salts
manufacturing	aluminum fluoride
beauty shop	persulfate
refinery workers	vanadium
welding	stainless steel fumes
	Organic Chemicals:
manufacturing	antibiotics, piperazine, methyl dopa, salbutanol, cimetidine
hospital workers	disinfectants (sulfathiazole, chloramine, formaldehyde, psyllium, glutaraldehyde)
anesthesiology	enflurane
poultry workers	aprollum
fur dyeing	paraphenylene diamine
rubber processing	formaldehyde, ethylene diamine, phthalic anhydride
plastics industry	tolulene diisocyanate, hexamethyl diisocyanate, dephenylmethyl isocyanate, phthalic anhydride, triethylene tetramines, trimellitic anhydride, hexamethyl tetramine
automobile painting	dimethyl ethanolamine toluene diisocyanate
foundry worker	furfuryl alcohol resin

■ **Outbreaks of asthma symptoms among other workers** may provide clues to the causative agent in an area of close exposure to the substance. Query the patient and, if the worker agrees, his or her medical officer at work about the possibility of other workers' symptoms.

■ **Objective documentation** should be obtained. It is preferable to monitor the patient's pulmonary function during normal work exposure rather than to perform an artificial exposure in the laboratory. The patient should monitor his or her peak expiratory flow rates (with the home peak flow meter) every 1-2 hours, from arising to retiring, during both working and nonworking days for 2-4 weeks. Measurements should also be made whenever symptoms occur, including during the night. Ideally, the monitoring period would include 1 week at work, 10 days away from the worksite, then 2 weeks at work. Significant variability in peak expiratory flow rates (greater than 20 percent) during work or in the evening, improvement over the weekend or during the week away from work, and deterioration on returning to work suggest that the symptoms are due to an adverse work environment.

■ **An occupational-type inhalation challenge with presumed sensitizers** is indicated in some cases. Consider this method when:

—Medicolegal issues of compensation for disability may require this level of documentation.

—The symptoms at work are too severe to warrant continued exposure.

—There is genuine doubt remaining after worksite and home monitoring (including doubt about whether the patient made accurate readings).

—Multiple agents are implicated.

—An agent not previously known to cause asthma is suspected.

An occupational-type inhalation challenge has risks. It should be conducted only by experienced specialists and only where resuscitation facilities are available and frequent observations can be made.

Managing Occupational Asthma

Treatment of acute and chronic occupational asthma should follow the guidelines given in previous sections. Early diagnosis and removal from exposure is associated with a favorable prognosis. Recommendations of particular importance in managing occupational asthma include eliminating exposure and referral to a specialist.

Eliminating exposure is the preferred treatment for occupational asthma because once sensitization has occurred, bronchoconstriction will often be triggered by minimal subsequent exposure. Furthermore, once well established, occupational asthma may not be completely reversible; recovery, if it occurs, may take months or even years, even after removal from exposure. Conversely, early diagnosis and removal from exposure is associated with a favorable prognosis.

Before recommending that a worker leave a job, ascertain if the job process or activities can be changed to reduce exposure; individual protective equipment may be useful. Immunotherapy may be indicated for veterinarians and workers exposed to laboratory animals. Furthermore, management of occupational asthma may require more than treatment of the individual worker. Complete management of the problem may involve careful review of the manufacturing process with a view to engineering changes to minimize exposures and establish a system of monitoring and surveillance for the protection of other workers.

Referral to a specialist. Diagnostic treatment as well as worker compensation and relocation issues warrant referral to an asthma specialist at the earliest suggestion of a relationship between symptoms of asthma and occupational exposure.

Rhinitis, Sinusitis, and Nasal Polyps

The nose prepares air for the lungs by adding moisture and by removing both particulate matter and gases. Maintenance of nasal patency and function will probably contribute to asthma control. Of particular current interest is the possible relation between sinusitis and activation of asthma. Consequently, treatment of sinusitis may lead to more effective control of asthma. It is also likely that nasal and sinus disease can aggravate asthma, particularly if there is uncontrolled drainage of mucoid or mucopurulent material down the nasopharynx where it can contribute to cough and irritability of the larynx. This material also may be aspirated into the lower airway, especially during sleep. It is also possible, but unproven, that sinus infection may lead to aggravation of asthma through reflex mechanisms.

Treatment Considerations

Treatment of the upper airway should include restoration of nasal patency, control of nasal secretions, and treatment of bacterial infection. Allergic patients should also avoid exposure to allergens and may consider immunotherapy. Preferred methods of treatment are:

Restoring patency. Only oral and topical nasal decongestants and corticosteroids improve nasal patency directly. This is achieved largely through an effect on the capacitance vessels of the turbinates. Cromolyn sodium nasal spray may have some effect by reducing the allergic response. Antihistamines are notably ineffective.

Controlling secretions. Thick and purulent nasal secretions may be temporarily removed by nasal lavage. Antihistamines decrease secretions through their effect on histamine-induced reflex secretion. For this reason, classic antihistamines, which possess anticholinergic properties as well, may be somewhat more effective than nonsedating antihistamines. Topical nasal corticosteroids decrease mucus secretion. The anticholinergic drug, ipratropium, has been reported to decrease watery discharge.

Treating sinus infections. An eosinophilic infiltrative hypertrophy of the paranasal sinus mucosa is often present in patients with asthma. It is likely that this mucosa is more susceptible to infections because of the loss of ciliated epithelium and the obstruction to drainage resulting from swelling about the ostia of the sinuses. A valuable clue to the presence of sinus infection is gross purulence of the nasal secretions (dark yellow-green) or predominance of neutrophils on nasal smear. Preferred therapy includes treatment for nasal mucosal edema and obstruction and antibiotics that are effective against the usual organisms of sinusitis. Consultation with an otolaryngologist may be beneficial.

Managing nasal polyps. Nasal polyps associated with asthma and rhinitis are seen primarily in patients who are over 40 years old. Nasal polyps are at least twice as prevalent in asthma and rhinitis patients who have negative skin tests as those with positive skin tests. This suggests that nasal polyps are probably a manifestation not of allergy but of the underlying eosinophilic hypertrophic sinusitis that accompanies severe asthma and rhinitis. Nasal polyps are remarkably responsive to corticosteroids. Sometimes, especially with large polyps, oral corticosteroids are needed for several weeks to cause regression of the polyps. Polyps that are not far advanced can be reduced by nasal steroids. Continuous, long-term administration of nasal steroids can maintain this improvement. Patients who have chronic nasal obstruction that persists in spite of treatment may benefit from surgery. Patients with nasal polyps should have spirometry with appropriate evaluation prior to surgery.

Aspirin Sensitivity

From 5 to 20 percent of adults with asthma will experience severe and even fatal exacerbations of bronchoconstriction after ingestion of aspirin or certain nonsteroidal anti-inflammatory drugs (NSAIDs) (see Figure 10-4). The prevalence increases with increasing severity of asthma.

The mechanism appears to be related to inhibition of the enzyme cyclooxygenase, a property common to all of the drugs producing this adverse reaction. Although analgesics not inhibiting cyclooxygenase are generally considered to be safe, the most frequently employed alternative, acetaminophen (Tylenol), has been reported to cause asthma exacerbations in a few aspirin-sensitive patients.

An association between aspirin sensitivity in people with asthma and the presence of sinusitis and nasal polyps is often stressed. Although there is a statistical correlation, many patients with nasal polyps are not aspirin sensitive, and more importantly, many patients with asthma who react adversely to aspirin have not been found to have nasal polyps. It is likely that sinusitis, nasal polyps, and aspirin sensitivity all increase in prevalence with increasing severity of asthma and that they are not causally related.

Even an initial reaction to aspirin or NSAIDs may be severe, and an adverse reaction may occur at any time, typically following years of employing these drugs without difficulty. Therefore, it is recommended that all patients with asthma be counseled to avoid this group of medications and to employ such usually safe alternatives as acetaminophen, sodium salicylate, or disalcid. Aspirin or an NSAID may be required on a regular basis for rheumatologic or other conditions. Reactions to these drugs produce a refractory state lasting 2-7 days and do not occur if patients ingest the drugs on a daily basis.[1] If the patient has been avoiding this class of drugs, it is wise to give the initial dose in the form of a rapid graded challenge in the physician's office. If the patient has severe asthma requiring steroids or has severe asthma with compromised pulmonary function, or if the patient reports a previous bronchoconstrictive reaction to these drugs, a more conservative treatment approach is indicated and should be undertaken by a physician familiar with the technique.[1] Aspirin use may be a special problem with patients with nasal polyps, chronic rhinosinusitis, and steroid dependency. If there is concern about use of aspirin in these patients, a sensitivity challenge should be conducted by a specialist.

Figure 10-4
Drugs Causing Reactions in Aspirin-Sensitive Patients*

Aspirin
Ibuprofen (Advil, Motrin)
Indomethacin (Indocin)
Piroxicam (Feldene)
Sulindac (Clinoril)
Tolmetin (Tolectin)
Naproxen (Naprosyn, Anaprox)
Fenoprofen (Nalfon)
Meclofenamate (Meclomen)
Mefenamic acid (Ponstel)
Diclofenac sodium (Voltaren)

**This list is not all inclusive. Many over-the-counter preparations contain aspirin. Furthermore, aspirin sensitivity implies cross-reactivity with other nonsteroidal medications.*

Sulfite Sensitivity

Sulfiting agents have been used to preserve foods and beverages since ancient times. They maintain the crisp and fresh appearance of foods, prevent browning, and control microbial growth and spoilage.[1] The agents employed include sulfur dioxide as well as the sodium and potassium salts of sulfite, bisulfite, and metabisulfite. All of these agents release sulfur dioxide gas under suitable conditions of warmth and acidity.

Pathophysiology

Exposure to sulfites, particularly in the setting of restaurant salad bars, has been incriminated in many severe and even fatal asthma exacerbations. Double-blind studies established that levels of sulfites commonly found in a restaurant meal could lead to sudden and severe bronchoconstriction in some people with asthma.[2]

Subsequent studies have incriminated sulfur dioxide released from sulfites in the mouth and perhaps also in the stomach as the precipitant of asthma in the vast majority of patients.[2] Sulfur dioxide is a known irritant to which asthmatics are particularly susceptible, and the levels released from the foods and beverages could easily account for the bronchoconstriction produced.

It remains unclear why all people with asthma do not respond adversely to sulfites. One variable may be the extent to which they inhale the liberated sulfur dioxide when eating and drinking. There may also be a subset of people with asthma who have low levels of the enzyme sulfite oxidase. These patients can less readily metabolize sulfites to harmless sulfates and thus are more susceptible to a large sulfite load. There appear also to be rare individuals with true allergy to sulfites, in whom immediate skin test reactivity to sulfite solutions can be demonstrated.

Sources of Exposure

When the potential seriousness of the sulfite problem was recognized, the food industry reduced the use of sulfites, and in 1986, the Food and Drug Administration (FDA) banned their use on fruits and vegetables served as "fresh." This has resulted in a major reduction in the potential exposure of people with asthma to sulfites, especially because it resulted in the removal of sulfites on lettuce in salad bars. Lettuce is a particularly dangerous source of exposure because of the amount of sulfites commonly added, the frequent associated use of citric acid, and the loose binding of the sulfites to lettuce.[3]

Although removed from salad bars by the FDA's order, sulfites may still be encountered in potatoes, where they are used to retard browning during preparation. Serious and even fatal reactions have been reported with potatoes processed in restaurants.

Major sources of exposure to sulfites that may still be encountered are:

Processed potatoes.

Shrimp.

Dried fruits.

Beer and wine.

Another source of sulfite exposure for patients with asthma is medication. Sulfites are employed to prevent oxidation of beta-adrenergic agonists. For this purpose, sulfites are contained in some nebulizer solutions (e.g., Bronkosol, Isuprel), injected epinephrine, and injected local anesthetics containing epinephrine. Except in the rare individual with true allergy to sulfites, the amount in the injected solutions is inconsequential. However, the amount in the nebulizer solutions is sufficient to cause paradoxical bronchoconstriction or at least blunted bronchodilator response in some individuals and should be avoided in the sulfite-sensitive patient.[3]

Diagnosis

Indications of sulfite sensitivity are a history of acute worsening of asthma immediately after drinking wine or beer, or unexplained worsening of asthma while eating in restaurants, particularly if the meal included processed potatoes. Specific diagnosis should be considered if the reaction was particularly severe. Diagnostic proof requires progressive challenge with solutions containing acidified sulfite. This procedure should be conducted by a physician knowledgeable in these challenges.

Tartrazine Sensitivity

Beginning in 1958, a number of reports appeared linking the yellow dye tartrazine, commonly employed in food and medication, with the occurrence of acute bronchoconstriction. This association was noted especially in those patients with asthma who also reacted adversely to aspirin. Although the reported prevalence varied greatly, there were reports of positive challenges in up to 22 percent of unselected asthma patients and in 25-50 percent of those with demonstrated sensitivity to aspirin. Subsequently, with more carefully controlled studies, it became apparent that these reports grossly overestimated the occurrence of tartrazine sensitivity in asthma patients and that most or all of these "reactions" were really decreases in pulmonary function tests that resulted from withholding bronchodilator drugs on the day of challenge.[1]

In one study, physicians challenged 150 patients with proven aspirin sensitivity. Although a few screening challenges were positive, they were not reproducible on a subsequent double-blind challenge and are thought to be a manifestation of unstable asthma rather than tartrazine sensitivity.[1] Other groups have also been unable to confirm the occur-

rence of tartrazine sensitivity. Furthermore, since tartrazine is not a cyclooxygenase inhibitor, no theoretic basis exists for it to produce bronchoconstriction in aspirin-sensitive asthma patients. The incidence of tartrazine-induced asthma must be very low and may be limited to those rare individuals who appear to have an immunologically mediated sensitivity to the dye.

Gastroesophageal Reflux

The prevalence of gastroesophageal reflux is increased at least threefold in both children and adults with bronchial asthma. Most of these patients also have a demonstrable hiatal hernia. This may contribute to the reflux by reducing the normal barrier function of the esophageal-gastric junction, as well as by impairing esophageal clearance of refluxed material.[1]

The relationship of asthma to gastroesophageal reflux remains a matter of debate.[1] In some studies, medical and surgical treatment of gastroesophageal reflux has resulted in improvement in symptoms of esophagitis and also a decrease in asthma symptoms, particularly those occurring at night. Other studies have failed to document similar beneficial effects on asthma. The situation is further complicated by the demonstration that induction of bronchoconstriction with methacholine can induce gastroesophageal reflux, indicating that occurrence of the two together does not necessarily mean the reflux is inducing bronchoconstriction. Indeed, when 100 patients with gastroesophageal reflux were monitored through the night, respiratory symptoms most commonly occurred independently of reflux; when the two were present, the reflux was as common following onset of asthma as it was preceding onset. When reflux does appear to lead to wheezing, the most probable mechanism is by reflex vagal bronchoconstriction secondary to stimulation of sensory nerve fibers in the lower esophagus. Microaspiration, once thought to be operative, has rarely been demonstrated.

Normal individuals may reflux up to 50 times in 24 hours, mostly in the 3 hours following meals. The refluxed material is rapidly cleared by gravity and swallowing and causes no symptoms. It is the absence of these clearance mechanisms at night that makes nocturnal reflux particularly likely to cause erosive esophagitis.

Diagnosis

In many patients with asthma, the diagnosis of esophagitis can be made by history alone with sufficient accuracy to justify institution of medical therapy. Symptoms include:

Excessive belching, burping, and spitting up in infants and small children.

Belching and heartburn in older children and adults.

Nocturnal exacerbations that do not respond to therapy.

Management

Medical management includes:

Physiologic and dietary measures, such as:

—Elevating the head of the bed 6-8 inches.

—Eating smaller but more frequent meals.

—Avoiding food or drink between dinner and bedtime.

Inhibition of gastric acid production using H-2 antagonists.

Maintenance of lower esophageal sphincter (LES) pressure by:

—Avoiding fatty meals, spices, ethanol, and methylxanthines (theophylline, caffeine).

—Employing drugs that increase LES pressure (e.g., metoclopromide).

Aggressive medical management from a specialist (e.g., gastroenterologist) may alleviate symptoms before referral for surgery is necessary.

Surgery is indicated for severely symptomatic esophagitis that is not responsive to medical therapy and for complications such as strictures. In the absence of these indications, surgery should be considered for respiratory complications of reflux only when the presence of nocturnal reflux clearly followed by pulmonary symptoms has been established. Because the surgery is extensive and is not successful for everyone, emphasis is on medical therapy.

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PROGLYCEM Suspension, 50 mg/ml, a chocolate-mint flavored suspension; bottle of 30 ml (NDC 0085-0426-04), with dropper calibrated to deliver 10, 20, 30, 40, and 50 mg diazoxide. **Shake well before each use. Protect from light. Store in carton until contents are used. Store PROGLYCEM Capsules and Suspension between 2° and 30°C (36° and 86°F).**

Animal Pharmacology and/or Toxicology: Oral diazoxide in the mouse, rat, rabbit, dog, pig, and monkey produces a rapid and transient rise in blood glucose levels. In dogs, increased blood glucose is accompanied by increased free fatty acids, lactate, and pyruvate in the serum. In mice, a marked decrease in liver glycogen and an increase in the blood urea nitrogen level occur.

In acute toxicity studies the LD_{50} for oral diazoxide suspension is >5000 mg/kg in the rat, >522 mg/kg in the neonatal rat, between 1900 and 2572 mg/kg in the mouse, and 219 mg/kg in the guinea pig. Although the oral LD_{50} was not determined in the dog, a dosage of up to 500 mg/kg was well tolerated.

In subacute oral toxicity studies, diazoxide at 400 mg/kg in the rat produced growth retardation, edema, increases in liver and kidney weights, and adrenal hypertrophy. Daily dosages up to 1080 mg/kg for three months produced hyperglycemia, an increase in liver weight and an increase in mortality. In dogs given oral diazoxide at approximately 40 mg/kg/day for one month, no biologically significant gross or microscopic abnormalities were observed. Cataracts, attributed to markedly disturbed carbohydrate metabolism, have been observed in a few dogs given repeated daily doses of oral or intravenous diazoxide. The lenticular changes resembled those which occur experimentally in animals with increased blood glucose levels. In chronic toxicity studies, rats given a daily dose of 200 mg/kg diazoxide for 52 weeks had a decrease in weight gain and an increase in heart, liver, adrenal and thyroid weights. Mortality in drug-treated and control groups was not different. Dogs treated with diazoxide at dosages of 50, 100 and 200 mg/kg/day for 82 weeks had higher blood glucose levels than controls. Mild bone marrow stimulation and increased pancreas weights were evident in the drug-treated dogs; several developed inguinal hernias, one had a testicular seminoma, and another had a mass near the penis. Two females had inguinal mammary swellings. The etiology of these changes was not established. There was no difference in mortality between drug-treated and control groups. In a second chronic oral toxicity study, dogs given milled diazoxide at 50, 100, and 200 mg/kg/day had anorexia and severe weight loss, causing death in a few. Hematologic biochemical, and histologic examinations did not indicate any cause of death other than inanition. After one year of treatment, there is no evidence of herniation or tissue swelling in any of the dogs.

When diazoxide was administered at high dosages concomitantly with either chlorothiazide to rats or trichlormethiazide to dogs, increased toxicity was observed. In rats, the combination was nephrotoxic; epithelial hyperplasia was observed in the collecting tubules. In dogs, a diabetic syndrome was produced which resulted in ketosis and death. Neither of the drugs given alone produced these effects.

Although the data are inconclusive, reproduction and teratology studies in several species of animals indicate that diazoxide, when administered during the critical period of embryo formation, may interfere with normal fetal development, possibly through altered glucose metabolism. Parturition was occasionally prolonged in animals treated at term. Intravenous administration of diazoxide to pregnant sheep, goats, and swine produced in the fetus an appreciable increase in blood glucose level and degeneration of the beta cells of the Islets of Langerhans. The reversibility of these effects was not studied.

Revised 6/83

PROVENTIL® Inhaler ℞
[*pro-ven' til*]
brand of albuterol
Bronchodilator Aerosol
FOR ORAL INHALATION ONLY

Description: The active component of PROVENTIL Inhaler is albuterol (α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol), a relatively selective $beta_2$-adrenergic bronchodilator. Albuterol is the official generic name in the United States. The international generic name for the drug is salbutamol. The molecular weight of albuterol is 239.3.

PROVENTIL Inhaler is a metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers from the mouthpiece 90 mcg of albuterol. Each canister provides at least 200 inhalations.

Clinical Pharmacology: The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. By virtue of its relatively selective action on $beta_2$-adrenoceptors, albuterol relaxes smooth muscle of the bronchi, uterus, and vascular supply to skeletal muscle, but may have less cardiac stimulant effects than does isoproterenol.

Albuterol is longer acting than isoproterenol by any route of administration in most patients because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation of recommended doses. Studies undertaken with four subjects administered tritiated albuterol, resulted in maximum plasma concentrations occurring within two to four hours. Due to the sensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72 percent of the inhaled dose is excreted within 24 hours in the urine, and consists of 28 percent of unchanged drug and 44 percent as metabolite.

Results of animal studies show that albuterol does not pass the blood-brain barrier.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that albuterol is ⅓ to ¼ as active as isoproterenol in producing increases in heart rate. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

Indications and Usage: PROVENTIL Inhaler is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. In controlled clinical trials the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximal midexpiratory flow rate (MMEF) and FEV_1. MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following 2 inhalations of albuterol and that clinically significant improvement generally continues for 3 to 4 hours in most patients. In clinical trials, some patients with asthma showed a therapeutic response (defined by maintaining FEV_1 values 15 percent or more above base line) which was still apparent at 6 hours. Continued effectiveness of albuterol was demonstrated over a 13-week period in these same trials.

Contraindications: PROVENTIL Inhaler is contraindicated in patients with a history of hypersensitivity to any of its components.

Warnings: As with other adrenergic aerosols, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

The contents of PROVENTIL Inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

Precautions: Although it has less effect on the cardiovascular system than isoproterenol at recommended dosages, albuterol is a sympathomimetic amine and as such should be used with caution in patients with cardiovascular disorders, including coronary insufficiency and hypertension, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes and ketoacidosis. The relevance of this observation to the use of PROVENTIL Inhaler is unknown, since the aerosol dose is much lower than the doses given intravenously.

Although there have been no reports concerning the use of PROVENTIL Inhaler during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information For Patients: The action of PROVENTIL Inhaler may last up to six hours and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking PROVENTIL Inhaler, other inhaled medicines should not be used unless prescribed.

See Illustrated Patient Instructions For Use.

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a 2 year study in the rat, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalational dose. The relevance of these findings to humans is not known. An 18-month study in mice revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects — Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg, corresponding to 1.4, 14, and 140 times the maximum human inhalational dose) showed cleft palate formation in 5 of 111 (4.5 percent) fetuses at 0.25 mg/kg and in 10 of 108 (9.3 percent) fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also

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A Clinical Trial of Long-Term Oral Salbutamol in Reversible Diffuse Airway Obstruction[1, 2]

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SUMMARY

A double blind, cross-over trial of the β_2-adrenergic stimulating drug, salbutamol, was carried out in 16 volunteers. The drug (2 mg) or placebo was administered as 1 tablet 4 times a day for 1 week and as 2 tablets 4 times a day for a second week. Daily diaries were kept that included readings of peak expiratory flow performed in triplicate twice a day. The active drug could be predicted based on the patient's assessment ($P < 0.01$), on the physician's assessment ($P < 0.01$), and improvement in the subject's peak expiratory flow ($P < 0.01$). Peak expiratory flow increased significantly ($P < 0.001$) for the group while taking salbutamol as compared with the placebo. No difference was noted between the week during which 2 mg of salbutamol was given 4 times a day and the week when 4 mg was given 4 times a day. Neuromuscular side effects were noted in 6 of the 16 subjects.

Introduction

Adrenergic drugs are important in the treatment of patients with reversible diffuse airway obstruction (1). This group of drugs is pharmacologically heterogeneous in that they have different activity in various tissues. This difference of activity is believed to be due to the presence of different adrenergic receptors. Ahlquist (2), in 1948, first postulated that there were 2 types of adrenergic receptors, namely, the α- and the β-receptors. The stimulation of the α-receptors is responsible, among other actions, for vasoconstriction, whereas the β-receptors are responsible for increase in heart rate and cardiac contractility and relaxation of bronchial muscle. In 1967, Lands and associates (3) suggested that there are both β_1- and β_2-receptors. The β_1-receptor is responsible for cardiac stimulation, whereas the β_2-receptor is responsible for the bronchial dilation. As a result of these findings, there has developed an interest in producing new drugs with selective β_2-stimulating effect. Such drugs should be safer for use in patients with reversible diffuse airway obstruction, particularly in those patients with cardiovascular disease.

One of the newer β_2-stimulating drugs is salbutamol (4). This drug is well absorbed orally (5) and has a long duration of activity (6). Extensive laboratory and clinical trials have demonstrated the effectiveness and safety of this drug for several hours after acute administration either orally or by inhalation (7–9); however, there is a lack of reliable

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clinical information on long-term oral therapy with salbutamol. It was therefore decided to carry out a double blind, clinical trial of salbutamol to compare its therapeutic and unwanted effects with those of a placebo during long-term, oral administration.

Materials and Methods

Only volunteers who had evidence of diffuse reversible airway obstruction were accepted for the study. The diagnosis of diffuse reversible airway obstruction was defined as a value less than 80 per cent of predicted (10–12) in at least one of the following parameters: forced expired volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF). These subjects had shown more than a 10 per cent improvement in at least one of these parameters after administration of 4 inhalations (640 μg) of isoproterenol hydrochloride from an aerosol inhaler.[3] Information regarding the subjects is included in table 1. Because measurements were made immediately before the placebo or salbutamol was administered, the observed values for FEV_1, FVC, and PEF in Subjects 7 and 8 were greater than 80 per cent of predicted normal. These values had previously been less than 80 per cent when the subjects were admitted to the trial. The mixed venous carbon dioxide tension ($P\bar{v}_{CO_2}$) ranged between 34 and 48 mm Hg (average: 41 mm Hg).

All subjects required some form of chronic

[3] Information on dosage was obtained from the Medical Director of Winthrop Laboratories, Canada.

TABLE 1

DATA FOR SUBJECTS OBSERVED WHEN TABLETS WERE FIRST ADMINISTERED

Subject Number	Clinical Diagnosis	Age (years)	Sex	FEV_1, liter (pred)	FEV_1, liter (obs)	FVC, liter (pred)	FVC, liter (obs)	PEF, liter/min (pred)	PEF, liter/min (obs)
1	Intrinsic asthma Pulmonary emphysema	69	M	3.2	0.5	4.0	1.7	520	105
2	Mixed asthma	42	F	2.6	1.0	3.1	2.7	415	170
3	Intrinsic asthma Chronic bronchitis Pulmonary emphysema	71	M	2.4	0.3	3.1	1.1	465	80
4	Intrinsic asthma Pulmonary emphysema	67	M	2.8	1.0	3.5	3.6	499	220
5	Intrinsic asthma	76	M	2.7	2.1	4.4	4.3	440	310
6	Intrinsic asthma	47	F	2.7	1.6	3.2	2.8	421	285
7	Extrinsic asthma	33	F	3.1	3.0	3.7	4.9	448	380
8	Mixed asthma	17	F	3.5	2.8	4.0	4.0	469	440
9	Intrinsic asthma	65	M	3.2	2.0	4.0	3.9	528	530
10	Intrinsic asthma Pulmonary emphysema	51	M	3.4	1.0	4.4	3.3	578	285
11	Intrinsic asthma Pulmonary emphysema	61	M	3.8	0.5	4.6	2.3	563	115
12	Intrinsic asthma Chronic bronchitis Pulmonary emphysema	62	M	3.2	0.5	3.9	2.6	527	130
13	Mixed asthma	38	F	3.2	0.9	3.8	2.6	463	135
14	Intrinsic asthma	65	M	2.6	0.8	3.2	2.4	490	175
15	Mixed asthma	31	M	4.6	3.6	5.3	5.9	630	485
16	Intrinsic asthma Pulmonary emphysema	62	M	2.4	0.4	3.0	1.1	482	75

Definition of abbreviations: pred = predicted normal value; obs = observed value.

treatment with an adrenergic drug for their disease but did not require any other agents, such as xanthines, corticosteroids, disodium cromoglycate or antimicrobial drugs. They were all in a stable clinical state before and during the trial. All subjects signed a consent form after full explanation of the study.

The drug or placebo was administered after 1 week was allowed for elimination of all previous adrenergic medication. The previous therapy was replaced by inhaled isoproterenol hydrochloride as necessary. The drug or placebo was given as 1 tablet 4 times a day for 1 week and as 2 tablets 4 times a day for the second week. Salbutamol was given for the first 2 weeks to one half of the subjects, and placebo was given to the other half. The salbutamol tablet contained 2 mg of the drug. Subjects recorded daily subjective and objective information in a diary. The diary included measurement of PEF (15) with a Wright peak flow meter (14) in triplicate on first arising in the morning and just before going to bed at night. The number of times the subject used the isoproterenol hydrochloride inhaler was also recorded on the daily diary and used as an index of the number of attacks.

Subjects were assessed clinically each week. At this time, the diary was collected and the peak flow meter was calibrated. Every second week, i.e., at the beginning and end of either salbutamol or placebo therapy, urinalysis, hematologic, and biochemical studies were done. These studies included hemoglobin, hematocrit, leukocyte count, fasting blood glucose, blood urea nitrogen, and total proteins, albumin, uric acid, cholesterol, calcium, inorganic phosphorus, total bilirubin, alkaline phosphatase, glutamic oxalocetic transaminase, and lactic dehydrogenase in the serum. Pulmonary function was assessed every second week and consisted of an FEV_1, FVC, PEF, maximal mid-expiratory flow (MMEF), maximal voluntary ventilation (MVV), lung volumes by the helium dilution technique, rebreathing $P\bar{v}CO_2$, and the steady state diffusing capacity for carbon monoxide (D_{LCO}). A 12-lead electrocardiogram was also recorded.

Results

Fourteen of 16 subjects completed the study. Two subjects (No. 2 and 13) had to discontinue the use of salbutamol because of significant neuromuscular side effects after taking the first tablet. Both of these patients had taken placebo for 2 weeks before taking their first dose of salbutamol.

The active drug was predicted before the code was broken (table 2). The prediction was analyzed statistically and a P value was derived assuming a binomial sample. Eleven patients felt their breathing improved while on the active drug. The physician correctly predicted the active drug in 11 subjects and incorrectly in 1. The daily PEF values, assessed statistically for the subject, using the t test for unpaired samples, were correct in 11 of the 16 subjects. The use of isoproterenol hydrochloride as an indication of the number of attacks was only correct in 4 subjects and incorrect in 1.

The daily PEF values for each patient were analyzed for the last 5 days of each week in the placebo and in the salbutamol period (table 3). Statistical analysis for the group, comparing placebo to salbutamol and 2 to 4 mg dosage, using the paired t test, is shown in table 4. The mean PEF for the 2 weeks on placebo was 232 liter per min, whereas on salbutamol, it was 251 liter per min ($P < 0.001$). Results comparing peak flow meter values while the subjects took 2 mg 4 times a day or 4 mg 4 times a day were not signifi-

TABLE 2

PREDICTION OF THE ACTIVE DRUG FOR 16 SUBJECTS

Basis of Prediction	Total (no.)	Correct (no.)	Incorrect (no.)	Correct Prediction (%)	P
Patient's prediction	11*	11	0	100	<0.01
Physician's prediction	12*	11	1	92	<0.01
PEF	11*	11	0	100	<0.01
No. of attacks	5*	4	1	80	NS†

*Only firm predictions were analyzed.
†NS = not significant.

TABLE 3

MEAN PEAK EXPIRATORY FLOW FOR THE SUBJECTS WHILE RECEIVING PLACEBO AND SALBUTAMOL

Subject No.	PEF with Placebo, liter/min			PEF with Salbutamol, liter/min		
	First Week	Second Week	First plus Second	First Week	Second Week	First plus Second
1	102	110	106	111	121	116
2	96	90	93			
3	102	103	103	118	115	117
4	175	169	172	186	208	197
5	328	334	331	357	359	358
6	264	273	269	275	298	287
7	394	360	377	363	369	366
8	372	399	386	408	420	414
9	383	414	399	421	417	419
10	206	205	206	260	257	259
11	109	109	109	100	115	108
12	116	115	116	121	125	123
13	117	106	112			
14	158	166	162	193	204	199
15	420	423	422	457	407	432
16	91	85	88	121	115	118
Total	230	233	232	249	252	251

cantly different. Results of biweekly pulmonary function studies are shown in table 5. None of these values were significantly different on statistical analysis.

Six of the 16 patients noted significant side effects. Trembling was noted in 3 subjects, headache and palpitations in 2, muscular cramps in 1, and emotional upset in 1. There were no significant abnormalities in the hematologic, biochemical, or urinalysis studies when comparing the pretrial, placebo, or salbutamol period.

There was no significant difference in the heart rate, blood pressure, or electrocardiogram while on the placebo or salbutamol when compared to the pretrial studies. There were nonspecific abnormalities in repolarization in the electrocardiogram in 2 patients taking salbutamol and in 1 taking placebo.

Discussion

This study supports previous reports (15–18) of the effectiveness of long-term oral salbutamol therapy in patients with reversible diffuse airway obstruction. The previous studies are difficult to interpret because the subjects remained on other bronchodilator medications during the evaluation. In this study, the only bronchodilator used by the subjects was the adrenergic drug being assessed and the occasional use of isoproterenol hydrochloride by inhaler for acute episodes of respiratory distress. The study revealed a significant difference, subjectively and objec-

TABLE 4

SIGNIFICANCE (P VALUE) OF THE DIFFERENCE BETWEEN PEAK EXPIRATORY FLOWS

Placebo versus salbutamol			Four-Tablet versus Eight-Tablet Dosage	
First Weeks	Second Weeks	Both Weeks	Placebo Weeks	Salbutamol Weeks
<0.01	<0.025	<0.001	NS*	NS*

*NS = not significant.

TABLE 5

RESULTS OF BIWEEKLY PULMONARY FUNCTION STUDIES AT THE END OF PLACEBO AND SALBUTAMOL ADMINISTRATION

Measurement	Placebo	Salbutamol	Change (%)
FEV_1, liter	1.44	1.56	+8
FVC, liter	3.19	3.39	+6
VC, liter	3.36	3.53	+5
FEV_1/FVC, %	42	43	+2
MMEF, liter/sec	0.67	0.78	+16
MVV, liter/min	65	72	+11
PEF, liter/min	248	272	+10
TLC, liter	7.8	6.91	−2
RV, liter	3.65	3.36	−8
FRC, liter	4.68	4.49	−4
RV/TLC, %	50	47	−6
P_{CO}, mm Hg	44	43	−2
DL_{CO}, ml/min/mm Hg	13.0	14.7	+13

tively, between the drug and the placebo. Although there was a significant difference in daily PEF between the 2 weeks of salbutamol therapy and the 2 weeks of placebo, there was no significant difference while receiving 2 mg 4 times a day and while receiving 4 mg 4 times a day. This differed from the findings of Parker and co-workers (18), who concluded that only 4 mg 4 times a day was effective. This difference may be due to the fact that their group received continuous corticosteroids and that the dose was altered in 5 of their 12 subjects during the study.

The objective assessment of the effectiveness of long-term therapy with bronchodilator drugs in patients with diffuse, reversible, airway obstruction is extremely difficult. This is due to the variable nature of the disease. Measurement of airway obstruction on an intermittent basis, such as once a week, can be misleading because of the possibility of measuring a "peak" or "valley" in the natural course of the illness, and this has proved to be of limited value in the past; however, multiple measurements each day, using the peak expiratory flow meter, has overcome this problem and gives reliable objective evidence (13). This method of frequent measurement of PEF supported the effectiveness of oral salbutamol as administered in this study, although the changes noted were not great and not apparent in every case.

Six of the 16 subjects had troublesome side effects. These were primarily related to muscular or neurologic symptoms. There are probably β-adrenergic receptors in skeletal muscles (19), and their stimulation may be responsible for tremor in man (20). In 2 cases, the patients refused to take a second dose of the medication because of side effects. By chance, both of these patients had previously taken the placebo for 2 weeks without side effects.

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